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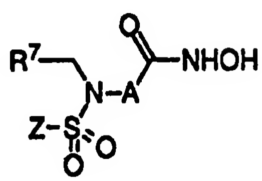

(I)

(57) Abstract

The present invention relates to the discovery of novel, low molecular weight, non-peptide inhibitors of matrix metalloproteinases (e.g. gelatinases, stromelysins and collagenases) and TNF-α converting enzyme (TACE, tumor necrosis factor-α converting enzyme) which are useful for the treatment of diseases in which theses enzymes are implicated such as arthritis, tumor growth and metastasis, angiogenesis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease, HIV infection, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization. The TACE and MMP inhibiting ortho-sulfonamido aryl hydroxamic acids of the present invention are represented by formula (I) where the hydroxamic acid moiety and the sulfonamido moiety are bonded to adjacent carbons of the heteroaryl ring of group A where: A is a 5-6 membered heteroaryl having from 1 to 3 heteroatoms independently selected from N, O and S fused to a phenyl ring, or another 5-6 membered heteroaryl having from 1 to 3 heteroatoms independently selected from N, O and S, and either; and Z, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are described in the specification, and the pharmaceutically acceptable salts thereof and the optical isomers and diastereomers thereof.

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ORTHO-SULFONAMIDO BICYCLIC HETEROARYL HYDROXAMIC ACIDS AS MATRIX METALLOPROTEINASE AND TACE INHIBITORS

Background of the Invention

The present invention relates to the discovery of novel, low molecular weight, non-peptide inhibitors of matrix metalloproteinases (e.g. gelatinases, stromelysins and collagenases) and TNF-α converting enzyme (TACE, tumor necrosis factor-α converting enzyme) which are useful for the treatment of diseases in which these enzymes are implicated such as arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system and HIV infection.

Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes [Woessner, J.F., Jr. *FASEB J.* **1991**, *5*, 2145; Birkedal-Hansen, H.; Moore, W.G.I.; Bodden, M.K.; Windsor, L.J.; Birkedal-Hansen, B.; DeCarlo, A.; Engler, J.A. *Crit. Rev. Oral Biol. Med.* **1993**, *4*, 197; Cawston, T.E. *Pharmacol. Ther.* **1996**, *70*, 163; Powell, W.C.; Matrisian, L.M. *Cur. Top. Microbiol. and Immunol.* **1996**, *213*, 1]. These zinc containing endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. Of these classes, the gelatinases have been shown to be the MMPs most intimately involved with the growth and spread of tumors, while the collagenases have been associated with the pathogenesis of osteoarthritis [Howell, D.S.; Pelletier, J.-P. In *Arthritis and Allied Conditions*; McCarthy, D.J.; Koopman, W.J., Eds.; Lea and Febiger: Philadelphia, **1993**; *12th Edition* Vol. *2*, pp. 1723; Dean, D.D. *Sem. Arthritis Rheum.* **1991**, *20*, 2; Crawford, H.C; Matrisian, L.M. *Invasion Metast.* **1994-95**, *14*, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, **1996**, *5*, 323].

It is known that the level of expression of gelatinase is elevated in malignancies, and that gelatinase can degrade the basement membrane which may lead to tumor metastasis [Powell, W.C.; Matrisian, L.M. *Cur. Top. Microbiol. and Immunol.* **1996**, *213*, 1; Crawford, H.C; Matrisian, L.M. *Invasion Metast.* **1994-95**, *14*, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, **1996**, *5*, 323; Himelstein, B.P.; Canete-Soler, R.; Bernhard, E.J.; Dilks, D.W.; Muschel, R.J. *Invasion Metast.* **1994-95**, *14*, 246; Nuovo, G.J.; MacConnell, P.B.; Simsir, A.; Valea, F.; French, D.L. *Cancer Res.*

1995, *55*, 267-275; Walther, M.M.; Levy, A.; Hurley, K.; Venzon, D.; Linehen, W.M.; Stetler-Stevenson, W. *J. Urol.* **1995**, *153 (Suppl. 4)*, 403A; Tokuraku, M; Sato, H.; Murakami, S.; Okada, Y.; Watanabe, Y.; Seiki, M. *Int. J. Cancer*, **1995**, *64*, 355; Himelstein, B.; Hua, J.; Bernhard, E.; Muschel, R.J. *Proc. Am. Assoc. Cancer Res. Ann. Meet.* **1996**, *37*, 632; Ueda, Y.; Imai, K.; Tsuchiya, H.; Fujimoto, N.; Nakanishi, I.; Katsuda, S.; Seiki, M.; Okada, Y. *Am. J. Pathol.* **1996**, *148*, 611; Gress, T.M.; Mueller-Pillasch, F.; Lerch, M.M.; Friess, H.; Buechler, M.; Adler, G. *Int. J. Cancer*, **1995**, *62*, 407; Kawashima, A.; Nakanishi, I.; Tsuchiya, H.; Roessner, A.; Obata, K.; Okada, Y. *Virchows Arch.*, **1994**, *424*, 547-552.]. Angiogenesis, required for the growth of solid tumors, has also recently been shown to have a gelatinase component to its pathology [Crawford, H.C; Matrisian, L.M. *Invasion Metast.* **1994-95**, *14*, 234; Ray, J.M.; Stetler-Stevenson, W.G. *Exp. Opin. Invest. Drugs*, **1996**, *5*, 323.]. Furthermore, there is evidence to suggest that gelatinase is involved in plaque rupture associated with atherosclerosis [Dollery, C.M.; McEwan, J.R.; Henney, A.M. *Circ. Res.* **1995**, *77*, 863; Zempo, N.; Koyama, N.; Kenagy, R.D.; Lea, H.J.; Clowes, A.W. *Arterioscler. Thromb. Vasc. Biol.* **1996**, *16*, 28; Lee, R.T.; Schoen, F.J.; Loree, H.M.; Lark, M.W., Libby, P. *Arterioscler. Thromb. Vasc. Biol.* **1996**, *16*, 1070.]. Other conditions mediated by MMPs are restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.

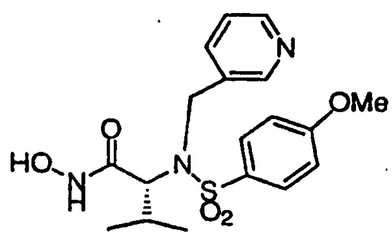
The hypothesis that MMPs are important mediators of the tissue destruction that occurs in arthritis has long been considered, since it was first recognized that these enzymes are capable of degrading collagens and proteoglycans which are the major structural components of cartilage [Sapolsky, A.I.; Keiser, H.; Howell, D.S.; Woessner, J.F., Jr.; *J. Clin. Invest.* **1976**, *58*, 1030; Pelletier, J.-P.; Martel-Pelletier, J.; Howell, D.S.; Ghandur-Mnaymneh, L.; Enis, J.E.; Woessner, J.F., Jr., *Arthritis Rheum.* **1983**, *26*, 63.], and continues to develop as new MMPs are identified. For example, collagenase-3 (MMP-13) was cloned from breast cancer cells in 1994, and the first report that it could be involved in arthritis appeared in 1995 [Freiji, J.M.; Diez-Itza, I.; Balbin, M.; Sanchez, L.M.; Blasco, R.; Tolivia, J.; Lopez-Otin, C. *J. Biol. Chem.* **1994**, *269*, 16766; Flannery, C.R.; Sandy, J.D. **102-17**, *41st Ann. Meet. Orth. Res. Soc.* Orlando, FL. February 13-16, 1995.].

Evidence is accumulating that implicates MMP-13 in the pathogenesis of arthritis. A major structural component of articular cartilage, type II collagen, is the preferred substrate for MMP-13 and this enzyme is significantly more efficient at cleaving type II collagen than the other collagenases [Knauper, V.; Lopez-Otin, C.; Smith, B.; Knight, G.; Murphy, G. *J. Biol. Chem.*, **1996**, *271*, 1544-1550; Mitchell, P.G.; Magna, H.A.; Reeves, L.M.; Lopresti-Morrow, L.L.; Yocum, S.A.; Rosner, P.J.; Geoghegan, K.F.; Hambor, J.E. *J. Clin. Invest.* **1996**, *97*, 761.]. MMP-13 is produced by chondrocytes, and elevated levels of MMP-13 has been found in human osteoarthritic tissues [Reboul, P.; Pelletier, J-P.; Hambor, J.; Magna, H.; Tardif, G.; Cloutier, J-M.; Martel-Pelletier, J. *Arthritis Rheum.* **1995**, *38 (Suppl. 9)*, S268;Shlopov, B.V.; Mainardi, C.L.; Hasty, K.A. *Arthritis Rheum.* **1995**, *38 (Suppl. 9)*, S313; Reboul, P.; Pelletier, J-P.; Tardif, G.; Cloutier, J-M.; Martel-Pelletier, J. *J. Clin. Invest.* **1996**, *97*, 2011]. Potent inhibitors of MMPs were described over 10 years ago, but the poor bioavailability of these early peptidic, substrate mimetic MMP inhibitors precluded their evaluation in animal models of arthritis. More bioavailable, non-peptidic MMP inhibitors may be preferred for the treatment of diseases mediated by MMPs.

TNF-α converting enzyme catalyzes the formation of TNF-α from membrane bound TNF-α precursor protein. TNF-α is a pro-inflammatory cytokine that is now thought to have a role in rheumatoid arthritis, septic shock, graft rejection, insulin resistance and HIV infection in addition to its well documented antitumor properties. For example, research with anti-TNF-α antibodies and transgenic animals has demonstrated that blocking the formation of TNF-α inhibits the progression of arthritis [Rankin, E.C.; Choy, E.H.; Kassimos, D.; Kingsley, G.H.; Sopwith, A.M.; Isenberg, D.A.; Panayi, G.S. *Br. J. Rheumatol.* **1995**, *34*, 334; *Pharmaprojects*, **1996**, Therapeutic Updates *17 (Oct.)*, au197-M2Z.]. This observation has recently been extended to humans as well. Other conditions mediated by TNF-α are congestive heart failure, cachexia, anorexia, inflammation, fever, inflammatory disease of the central nervous system, and inflammatory bowel disease.

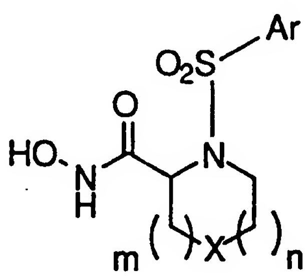
It is expected that small molecule inhibitors of gelatinase and TACE therefore have the potential for treating a variety of disease states. While a variety of MMP and TACE inhibitors have been identified and disclosed in the literature, the vast majority of these molecules are peptidic or peptide-like compounds that may have bioavailability and pharmacokinetic problems that would limit their clinical effectiveness. Low molecular weight, potent, long-acting, orally bioavailable inhibitors of gelatinases, collagenases and/or TACE are therefore highly desirable for the potential chronic treatment of the above mentioned disease states. Several non-peptidc, sulfur-containing hydroxamic acids have recently been disclosed and are listed below.

U. S. patents 5,455,258, 5,506,242 and 5,552,419, as well as European patent application EP606,046A1 and WIPO international publications WO96/00214 and WO97/22587 disclose non-peptide matrix metalloproteinase inhibitors of which the compound CGS27023A is representative. The discovery of this type of MMP inhibitor is further detailed by MacPherson, *et. al.* in *J. Med. Chem.*, (1997),40, 2525. Additional publications disclosing sulfonamide based MMP inhibitors which are variants of the sulfonamide-hydroxamate shown below, or the analogous sulfonamide-carboxylates, are European patent application EP-757984-A1 and WIPO international publications WO95/35275, WO95/35276, WO96/27583, WO97/19068 and WO97/27174.

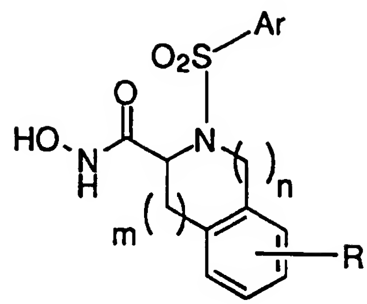


CGS 27023A

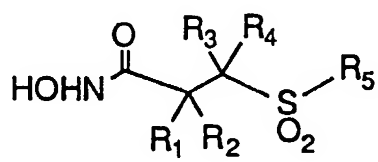
Publications disclosing β-sulfonamide-hydroxamate MMP inhibitor analogs of CGS 27023A in which the carbon alpha to the hydroxamic acid has been joined in a ring to the sulfonamide nitrogen, as shown below, include WIPO international publications WO96/33172 and WO97/20824.



The German patent application DE19,542,189-A1 discloses additional examples of cylic sulfonamides as MMP inhibitors. In this case the sulfonamide-containing ring is fused to a phenyl ring to form an isoquinoline.

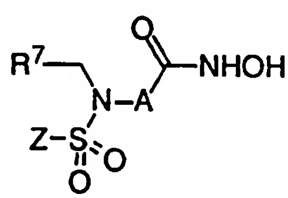


Analogs of the sulfonamide-hydroxamate MMP inhibitors in which the sulfonamide nitrogen has been replaced by a carbon atom, as shown in the general structure below, are European patent application EP-780386-A1 and WIPO international publication WO97/24117.



Summary of the Invention

The TACE and MMP inhibiting ortho-sulfonamido aryl hydroxamic acids of the present invention are represented by the formula



where the hydroxamic acid moiety and the sulfonamido moiety are bonded to adjacent carbons of group A where:

A is a 5-6 membered heteroaryl having from 1 to 2 heteroatoms independently selected from N, O, and S, and substituted by R^1 and R^2 on adjacent carbons wherein R^1 and R^2 together with the carbons to which they are attached form a fused phenyl ring or a 5-6 membered heteroaryl ring having from 1 to 3 heteroatoms selected independently from N, O and S, wherein either ring can be substituted by one or more substituents selected from R^4;

Z is aryl, heteroaryl, or heteroaryl fused to a phenyl,

where aryl is phenyl or naphthyl optionally substituted by R^1, R^2, R^3 and R^4;

heteroaryl is a 5-6 membered heteroaromatic ring having from 1 to 3 heteroatoms independently selected from N, O, and S, and optionally substituted by R^1, R^2, R^3 and R^4;

and when heteroaryl is fused to phenyl, either or both of the rings can be optionally substituted by R^1, R^2, R^3 and R^4;

R^1, R^2, R^3 and R^4 are independently -H, -COR^5, -F,-Br, -Cl, -I, -C(O)NR^5OR^6,-CN, -OR^5,-C_1-C_4-perfluoroalkyl, -$S(O)_xR^5$ where x is 0-2, -OPO(OR^5)OR^6, -PO(OR_6)R_5, -OC(O)NR^5R^6, -$COOR^5$, -$CONR^5R^6$, -SO_3H, -NR^5R^6, -NR^5COR^6, -NR^5COOR^6, -$SO_2NR^5R^6$, -NO_2, -N(R^5)SO_2R^6, -$NR^5CONR^5R^6$, -$NR^5C(=NR^6)NR^5R^6$, 3–6 membered cycloheteroalkyl having one to three heteroatoms independently selected from N, O, and S and optionally having 1 or 2 double bonds and optionally substituted by one to three groups each selected independently from R^5; -aryl or heteroaryl as defined above, -SO_2NHCOR^5or -$CONHSO_2R^5$ where R^5 is not H;
-tetrazol-5-yl, -SO_2NHCN, -$SO_2NHCONR^5R^6$ or straight chain or branched -C_1-C_6 alkyl, -C_2-C_6-alkenyl, or -C_2-C_6-alkynyl, or -C_3-C_6-cycloalkyl optionally having 1 or 2 double bonds each optionally substituted with -COR^5, -CN, -C_2-C_6 alkenyl, -C_2-C_6 alkynyl,-OR^5, -C_1-C_4-perfluoroalkyl, -$S(O)_xR^5$ where x is 0-2, -OC(O)NR^5R^6, -$COOR^5$, -$CONR^5R^6$, -SO_3H, -NR^5R^6,-NR^5COR^6, -NR^5COOR^6, -$SO_2NR^5R^6$, -NO_2, -N(R^5)SO_2R^6, -$NR^5CONR^5R^6$, -C_3-C_6 cycloalkyl as defined above, 3-6 membered cycloheteroalkyl as defined above, aryl or heteroaryl as defined above, -SO_2NHCOR^5 or-$CONHSO_2R^5$ where R^5 is not hydrogen, -PO(OR^5)OR^6, -PO(OR^6)R^5, -tetrazol-5-yl, -C(O)NR^5OR^6, -$NR^5C(=NR^6)NR^5R^6$,-$SO_2NHCONR^5R^6$ or -SO_2NHCN;

R^5 and R^6 are independently defined as H, aryl and heteroaryl as defined above, -C_3-C_6-cycloalkyl as defined above, -C_3-C_6-cycloheteroalkyl as defined above, -C_1-C_4-perfluoroalkyl, or straight chain or branched -C_1-C_6 alkyl, -C_2-C_6-alkenyl, or -C_2-C_6-alkynyl each optionally substituted with -OH, -COR^8, -CN, -C(O)NR^8OR^9, -C_2-C_6-alkenyl, -C_2-C_6-alkynyl,

$-OR^8$, $-C_1$-C_4-perfluoroalkyl, $-S(O)_xR^8$ where x is 0–2, $-OPO(OR^8)OR^9$, $-PO(OR^8)R^9$, $-OC(O)NR^8R^9$, $-COOR^8$, - $-CONR^8R^9$, $-SO_3H$, $-NR^8R^9$,$-NCOR^8R^9$, $-NR^8COOR^9$, $-SO_2NR^8R^9$, $-NO_2$, $-N(R^8)SO_2R^9$, $-NR^8CONR^8R^9$, $-C_3$-C_6 cycloalkyl as defined above, $-C_3$-C_6- cycloheteroalkyl as defined above, -aryl or heteroaryl as defined above, $-SO_2NHCOR^8$ or $-CONHSO_2R^8$ where R^8 is not hydrogen, -tetrazol-5-yl, - $-NR^8C(=NR^9)NR^8R^9$, $-SO_2NHCONR^8R^9$, or $-SO_2NHCN$;

R^7 is hydrogen, straight chain or branched $-C_1$-C_6-alkyl, $-C_2$-C_6-alkenyl, or $-C_2$-C_6-alkynyl each optionally substituted with -OH, $-COR^5$, -CN, $-C_2$-C_6-alkenyl, $-C_2$-C_6-alkynyl, $-OR^5$, $-C_1$-C_4-perfluoroalkyl, $-S(O)_xR^5$ where x is 0-2, $-OPO(OR^5)OR^6$, $-PO(OR^5)R^6$, $-OC(O)NR^5R^6$, - $COOR^5$, $-CONR^5R^6$, $-SO_3H$, $-NR^5R^6$,$-NR^5COR^6$, $-NR^5COOR^6$, - $SO_2NR^5R^6$, $-NO_2$, $-N(R^5)SO_2R^6$, $-NR^5CONR^5R^6$, $-C_3$-C_6 cycloalkyl as defined above, $-C_3$-C_6-cycloheteroalkyl as defined above, -aryl or heteroaryl as defined above, $-SO_2NHCOR^5$ or - $CONHSO_2R^5$ where R^5 is not hydrogen, -tetrazol-5-yl, - $NR^5C(=NR6)NR^5R^6$, $-C(O)N\ R^5OR^6$, $-SO_2NHCONR^5R^6$ or - SO_2NHCN;

or R^7 is phenyl or naphthyl, optionally substituted by R^1, R^2, R^3 and R^4 or a 5 to 6 membered heteroaryl group having 1 to 3 heteroatoms selected independently from N, O, and S and optionally substituted by R^1, R^2, R^3 and R^4;

or R^7 is C_3-C_6 cycloalkyl or 3-6 membered cycloheteroalkyl as defined above;

or R^7CH_2-N-A-, where A is as defined above, can form a non-aromatic 7-12 membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and N wherein said heterocyclic ring may be optionally fused to another benzene ring;

R^8 and R^9 are independently H, aryl or heteroaryl as defined above, $-C_3$-C_7-cycloalkyl or cycloheteroalkyl as defined above, $-C_1$-C_4-perfluoroalkyl, straight chain or branched $-C_1$-C_6-alkyl, $-C_2$-C_6-alkenyl, or $-C_2$-C_6-alkynyl, each optionally substituted with hydroxy, alkoxy, aryloxy, $-C_1$-C_4-perfluoroalkyl, amino, mono- and di-C_1-C_6-alkylamino, carboxylic

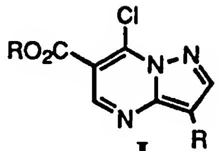
acid, carboalkoxy and carboaryloxy, nitro, cyano, carboxamido primary, mono- and di-C_1-C_6-alkylcarbamoyl;

and the pharmaceutically acceptable salts thereof and the optical isomers and diastereomers thereof.

Preferred compounds are those wherein both of the carbons of A adjacent to the carbon bearing the sulfonamido group have a substituent other than hydrogen. Also preferred are compounds where Z is 4-alkoxyphenyl, 4-aryloxyphenyl or 4-heteroaryloxyphenyl.

The term "heteroaryl" as defined hereinabove includes, but is not limited to, pyrrole, furan, thiophene, pyridine, pyrimidine, pyridazine, pyrazine,triazole, pyrazole, imidazole, isothiazole, thiazole, isoxazole and oxazole. The term "heteroaryl fused to a phenyl" includes, but is not limited to, indole, isoindole, benzofuran, benzothiophene, quinoline, isoquinoline, quinoxaline, quinazoline, benzotriazole, indazole, benzimidazole, benzothiazole, benzisoxazole, and benzoxazole.

The following compounds (I-XXI) which may be used in preparing compounds of the invention are known and references are given hereinbelow.



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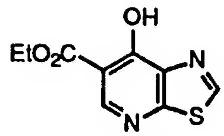

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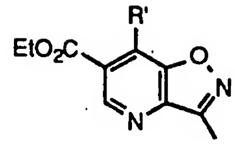

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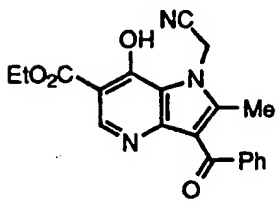

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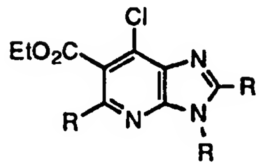

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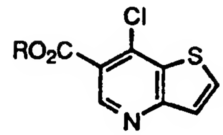

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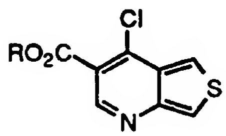

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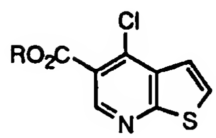

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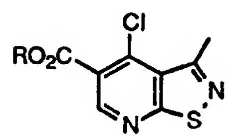

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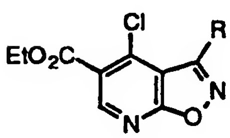

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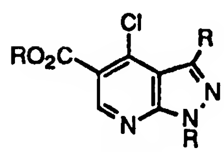

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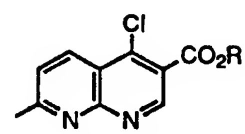

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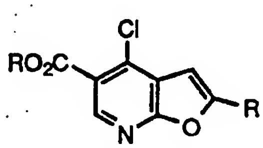

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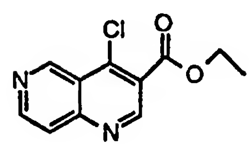

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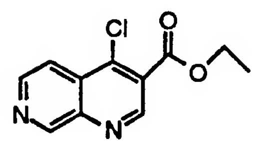

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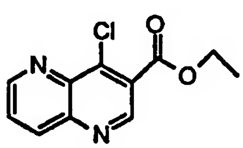

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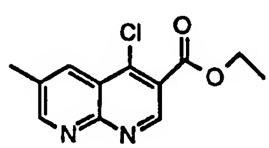

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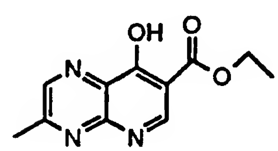

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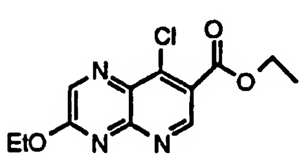

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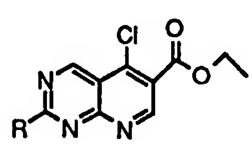

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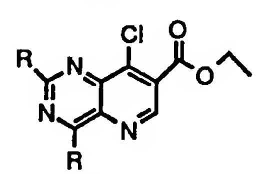


XXI

Compound I:

a) Springer, RH; Scholten, MB; O'Brien, DE, Novinson, T; Miller, JP; Robins, RK **J. Med. Chem.** (1982), 25(3), 235-42.

b) Elworthy, T.R.; Ford, A.P.D.; et.al. **J. Med. Chem.** (1997), 40(17), 2674-2687.

Compound II:

Masui, T; TAkura, T; **JP 46043792**; JP 690307; CAN 76:59604

Compound III:

Camparini, A; Ponticelli, F; Tedeschi, **P J. Chem. Soc., Perkin Trans.1** (1982), 10, 2391-4.

Compound IV:

Abdalla, GM; Sowell. JW **J. Heterocycl. Chem.** (1990), 27 (5), 1201-7.

Compound V:

a) Denzel, T; Hoehn, H **J. Heterocyclic Chem.** (1977), 14, 813-817.

b) Al-Shaar, AHM; Chambers, RK; Gilmour, DW; Lythgoe, DJ; McClenaghan, I; Ramsden, CA **J. Chem. Soc.; Perkin Trans. I** (1992) 21, 2789-2812.

c) Elworthy, T.R.; Ford, A.P.D.; et.al. **J. Med. Chem.** (1997), 40(17), 2674-2687.

Compound VI:

a) Forbes, IT; Johnson, CN; Jones, GE; Loudon, J; Nicholass, JM **J. Med. Chem** (1990) 2640- 2645.

b) Kan, MA; Guarconi, AE **J. Heterocyclic Chem** (1977) 14, 807-812.

Compound VII:

a) Forbes, IT; Johnson, CN; Jones, GE; Loudon, J; Nicholass, JM **J. Med. Chem** (1990) 2640- 2645.

b) Kan, MA; Guarconi, AE **J. Heterocyclic Chem** (1977) 14, 807-812.

Compound VIII:

Richardson, TO; Neale, N; Carwell, N **J. Heterocyclic. Chem.** (1995), 32, 359-361.

Baker, JM; Huddleston, PR; Keenan, GJ **J. Chem Research Miniprint**, (1982) 6, 1726-1746.

Compound IX:

a) Forbes, IT; Johnson, CN; Jones, GE; Loudon, J; Nicholass, JM **J. Med. Chem** (1990) 2640- 2645.

b) Kan, MA; Guarconi, AE **J. Heterocyclic Chem** (1977) 14, 807-812.

Compounds X, XI and XII:

Elworthy, T.R.; Ford, A.P.D.; et.al. **J. Med. Chem.** (1997), 40(17), 2674-2687.

Compound XIII:

Heterocycles, (1997), 45, 980.

Compound XIV:

Yokoyama, Naokata. Eur. Pat. Appl., 61 pp. CODEN: EPXXDW. **EP 115469 A1** 840808.

Compound XV:

Mendes, Etienne; Vernieres, Jean Claude; Simiand, Jacques Edouard; Keane, Peter Eugene. Eur. Pat. Appl., 12 pp. CODEN: EPXXDW. **EP 346207 A1** 891213.

Compound XVI:

Mendes, Etienne; Vernieres, Jean Claude; Simiand, Jacques Edouard; Keane, Peter Eugene. Eur. Pat. Appl., 12 pp. CODEN: EPXXDW. **EP 346207 A1** 891213.

Compound XVII:

Morita, Yoshiharu; Wagatsuma, Kazuo. Japan. Kokai, 4 pp. CODEN: JKXXAF. **JP 50058094** 750520 Showa.

Compounds XVIII and XIX:

Armitage, Bernard John; Leslie, Bruce William; Miller, Thomas Kerr; Morley, Christopher. PCT Int. Appl., 110 pp. CODEN: PIXXD2. **WO 9500511 A1** 950105.

Compound XX:

Minami, S.; Matsumoto, J.; Kawaguchi, K.; Mishio, S.; Shimizu, M.; Takase, Y.; Nakamura, S. (Dainippon Pharmaceutical Co., Ltd., Japan) Japan. Kokai, 3pp. CODEN: JKXXAF. **JP 50014697** 750215 Showa.

Compound XXI:

Kihara, N.; Tan, H.; Takei, M.; Ishihara, T. (Mitsui Pechochemical Industries, Ltd., Japan; Suntory, Ltd.) Jpn. Kokai Tokyo Koho,, 11pp. CODEN: JKXXAF. **JP 62221686 A2** 870929 Showa.

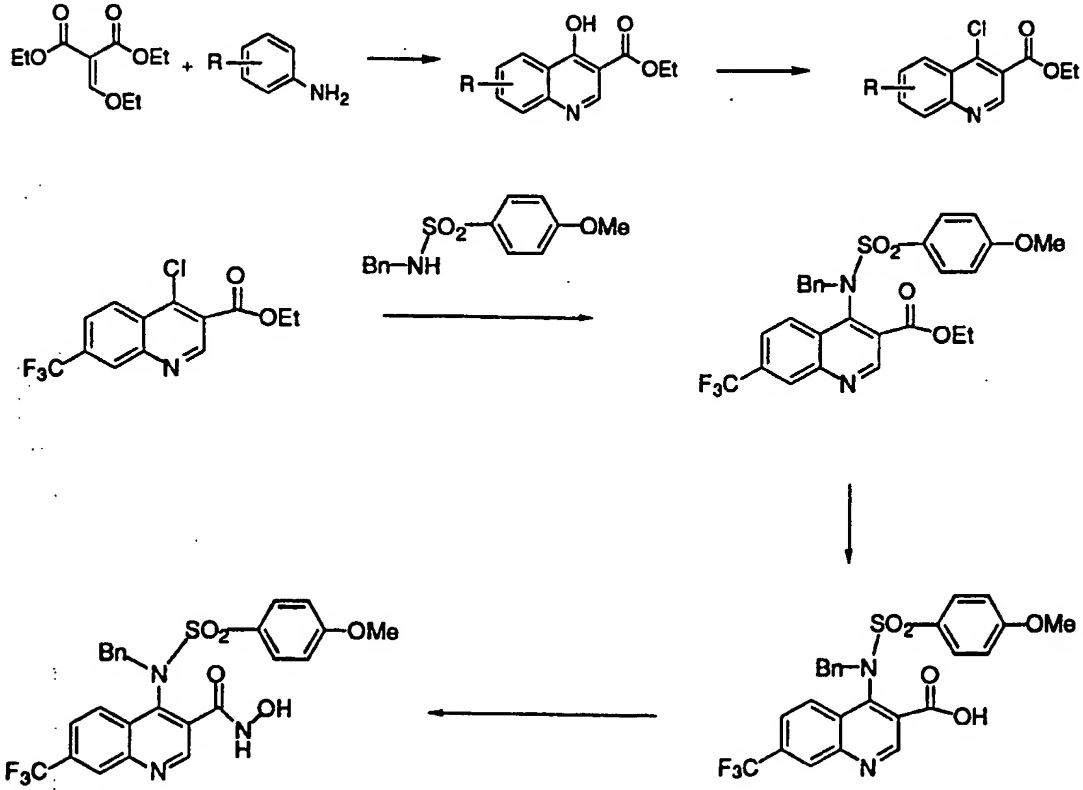
The compounds of this invention are shown to inhibit the enzymes MMP-1, MMP-9, MMP-13 and TNF-α converting enzyme (TACE) and are therefore useful in the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, graft rejection, insulin resistance, bone disease and HIV infection.

Detailed Description of the Invention

The invention compounds are prepared using conventional techniques known to those skilled in the art of organic synthesis. The following scheme (Scheme I) illustrates the reaction sequence employed. For purposes of illustration only, wherein the bicyclic heteroaryl group A shown is a quinoline, 4-chloro-7-trifluoromethylquinoline-3-carboxylic acid ethyl ester, prepared from the corresponding aniline, is reacted with *N*-benzyl-p-methoxybenzenesulfonamide, wherein Z is p-methoxybenzene, to provide the requisite *N,N*-disubstituted sulfonamido-ester which is then converted into the corresponding hydroxamic acid in two steps.

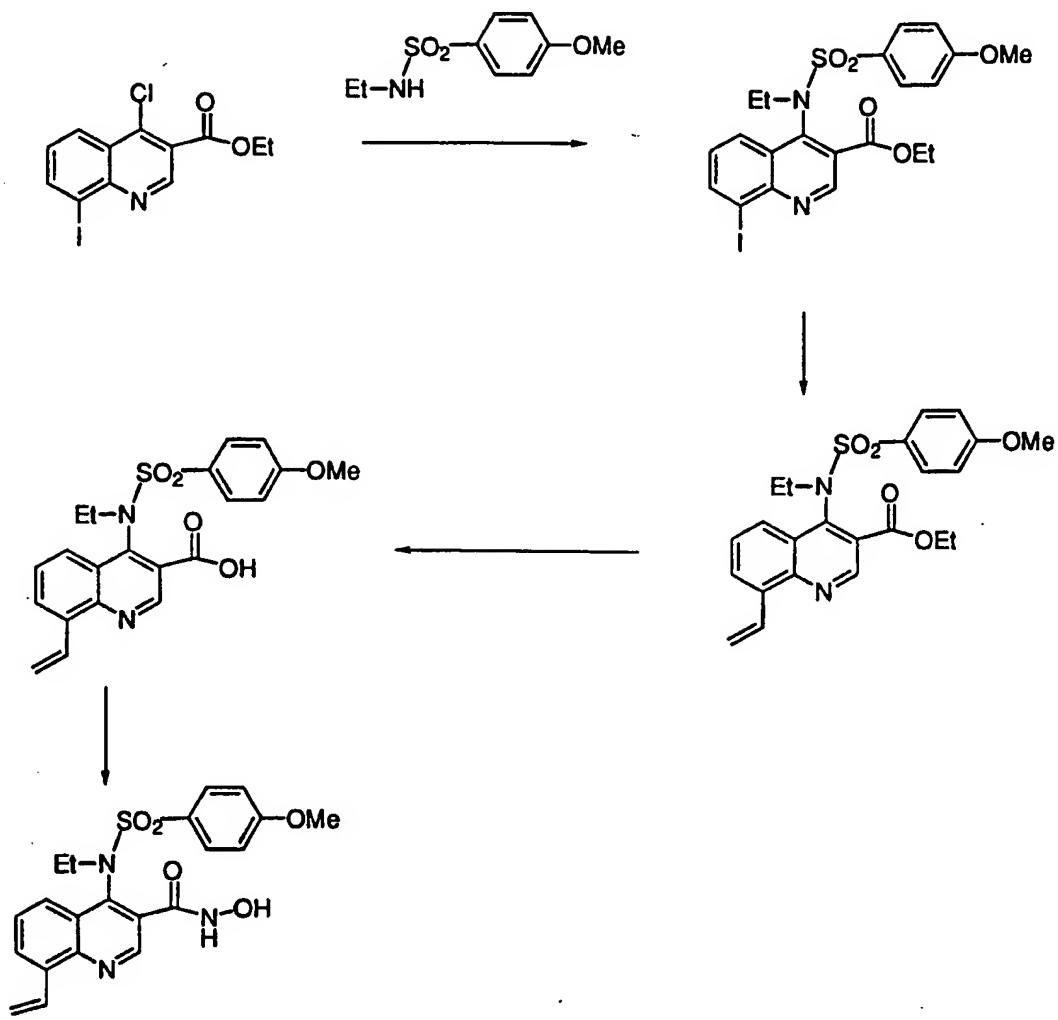
Alternatively, the 4-chloroquinoline carboxylic acid ester could be first reacted with R^7-NH_2 and the resulting 4-(R^7-amino)quinoline carboxylic acid ester then reacted with the appropriate Z-SO_2-Cl. Hydrolysis of the ester and reaction with hydroxylamine hydrochloride would then give the invention compound.

Scheme I.



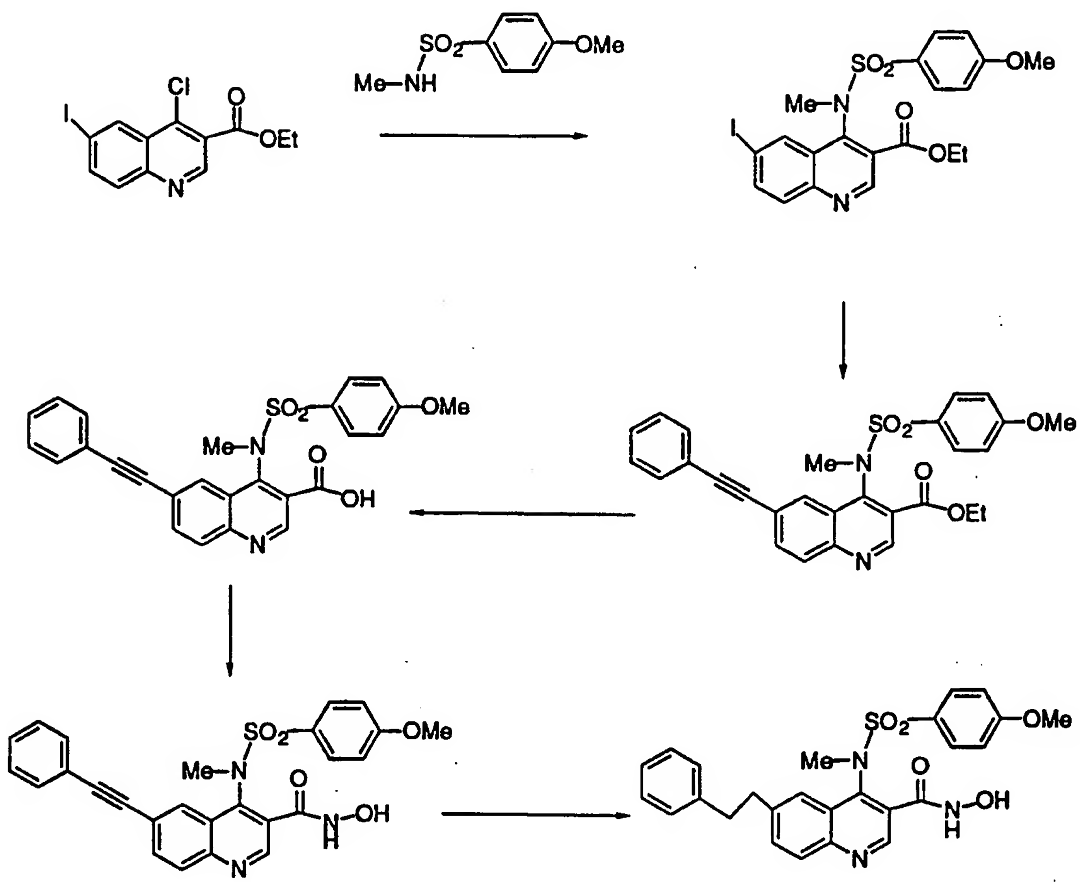
Functionalization of the quinoline ring via a palladium catalyzed Heck coupling between the iodoquinoline and tributylvinyltin is shown in Scheme II. α,β-Unsaturated esters and amides can be coupled to the haloquinoline via Heck reactions. A variety of other trialkyltin reagents are readily available and may be similarly used. Boronic acids, commercially available or readily prepared, may also be coupled to the iodoquinoline using the Suzuki reaction.

Scheme II.



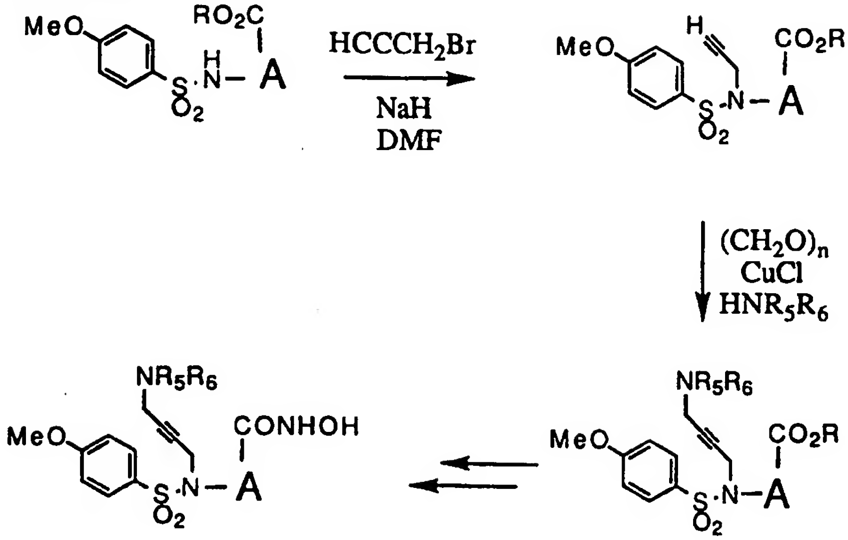
Functionalization of haloquinolines may also be accomplished via palladium catalyzed couplings of alkynes, as illustrated in Scheme III. Hydrogenation of the alkynes accesses the olefins and alkanes as well.

Scheme III.



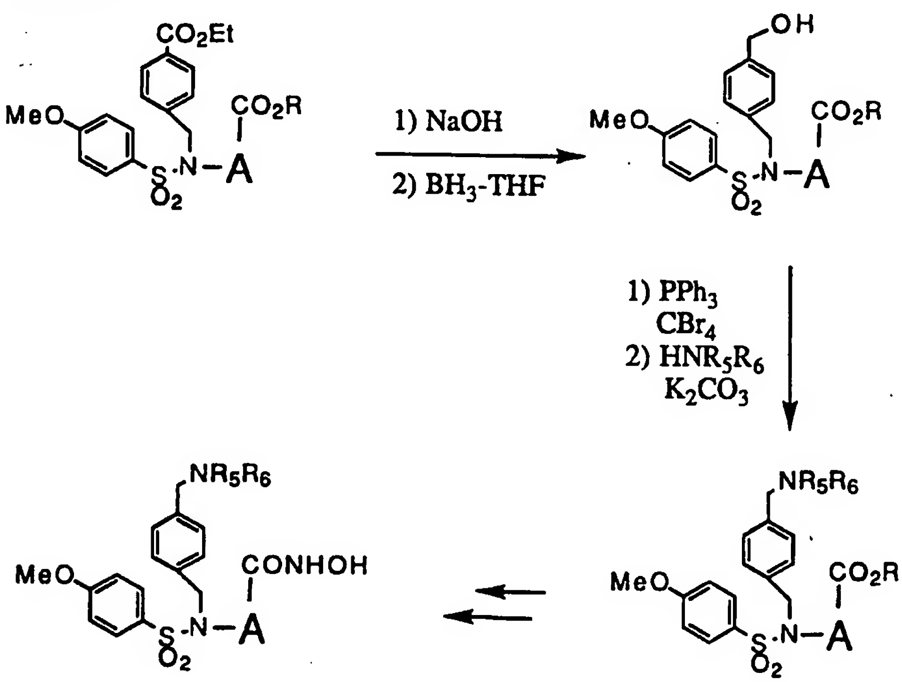
Schemes IV and V illustrate two methods for incorporating amino groups into the substituent attached to the sulfonamide nitrogen of the compounds of the invention. Thus, in Scheme IV the NH-sulfonamide is alkylated with propargyl bromide to provide the propargyl sulfonamide. This alkyne is reacted with paraformaldehyde in the presence of a primary or secondary amine and cuprous chloride to give the propargyl amine which is converted, as before, to the desired hydroxamic acid.

Scheme IV.



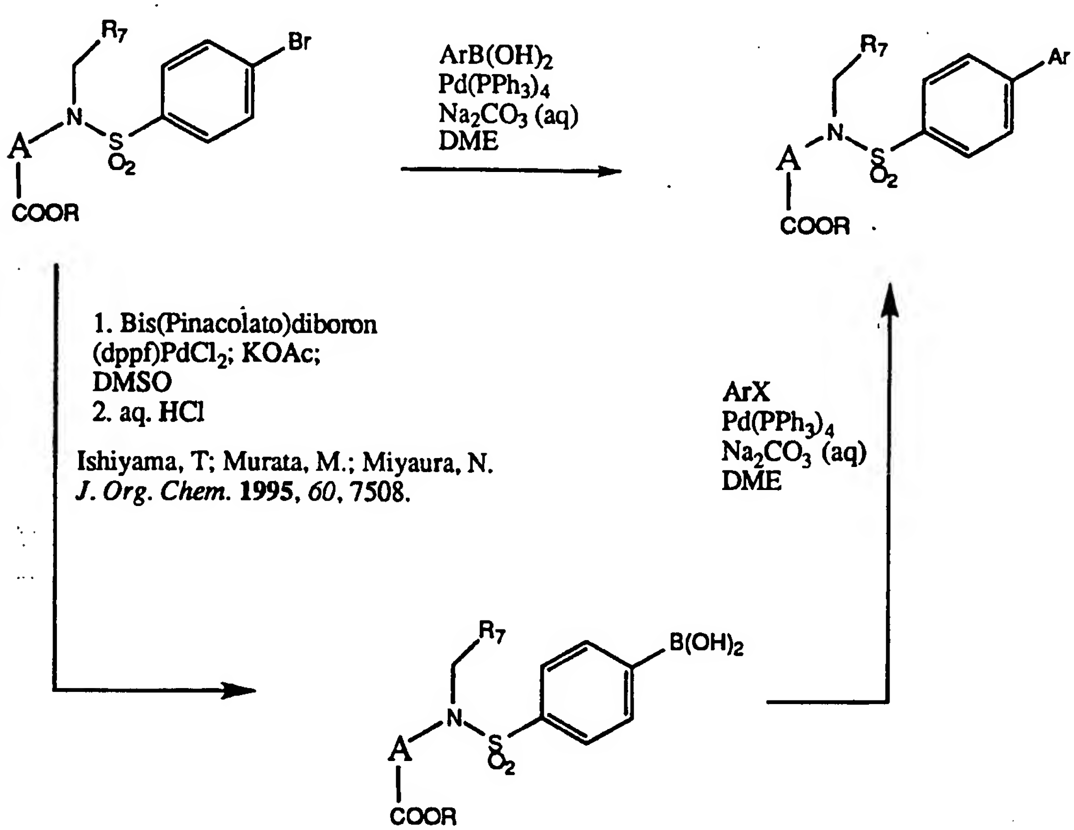
In Scheme V, selective hydrolysis of the ester of the p-carboethoxybenzyl sulfonamide group provides a mono-carboxylic acid. This acid may be converted into an amide (not shown), followed by conversion of the second ester, A-CO_2R, into the corresponding hydroxamate, or reduced to the corresponding alcohol with diborane. The alcohol may be converted into the analogous amine via the benzylic bromide, followed by conversion of the the ester, A-CO_2R, into the corresponding hydroxamate.

Scheme V.



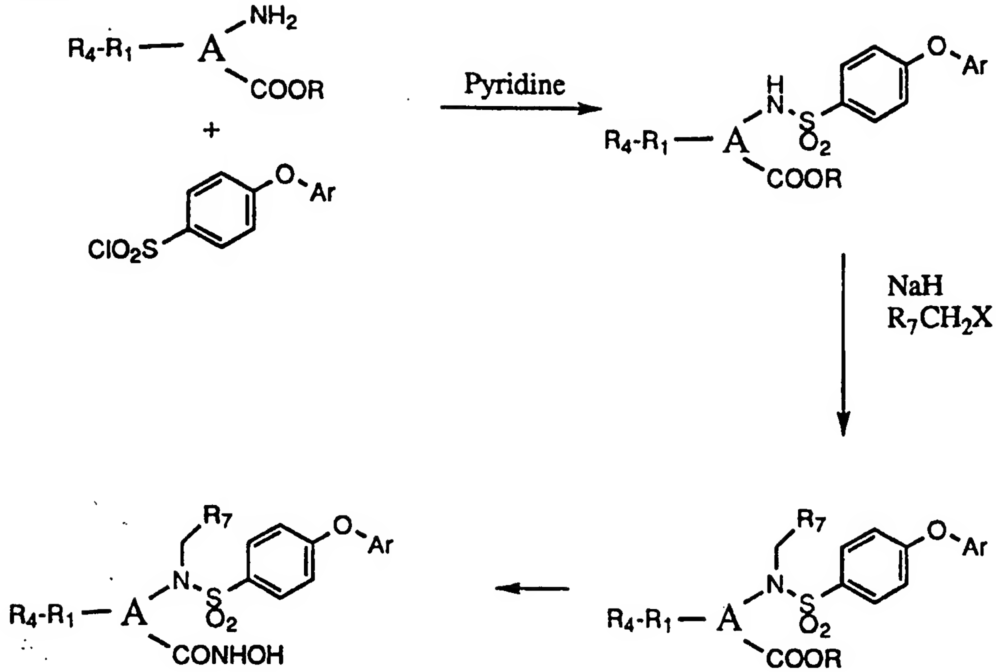
Methods for synthesizing variations of substituents on the sulfonyl aryl group are shown in Schemes VI through VIII. As shown in Scheme VI, biaryl sulfonyl groups are synthesized by Suzuki couplings on a bromo-substituted benzene sulfonamide. The starting bromo-substituted benzene sulfonamide is synthesized from the commercially available bromobenzenesulfonyl chloride and the amino-acid or amino-ester, $H_2N\text{-}A\text{-}CO_2R$, followed by alkylation of the resulting NH-sulfonamide. Alternatively, the bromo aryl sulfonamide is converted into the corresponding boronic acid by the method of Ishiyama, et.al. [J. Org. Chem. (1995), 60, 7508] followed by coupling with an appropriate aryl halide.

Scheme VI.



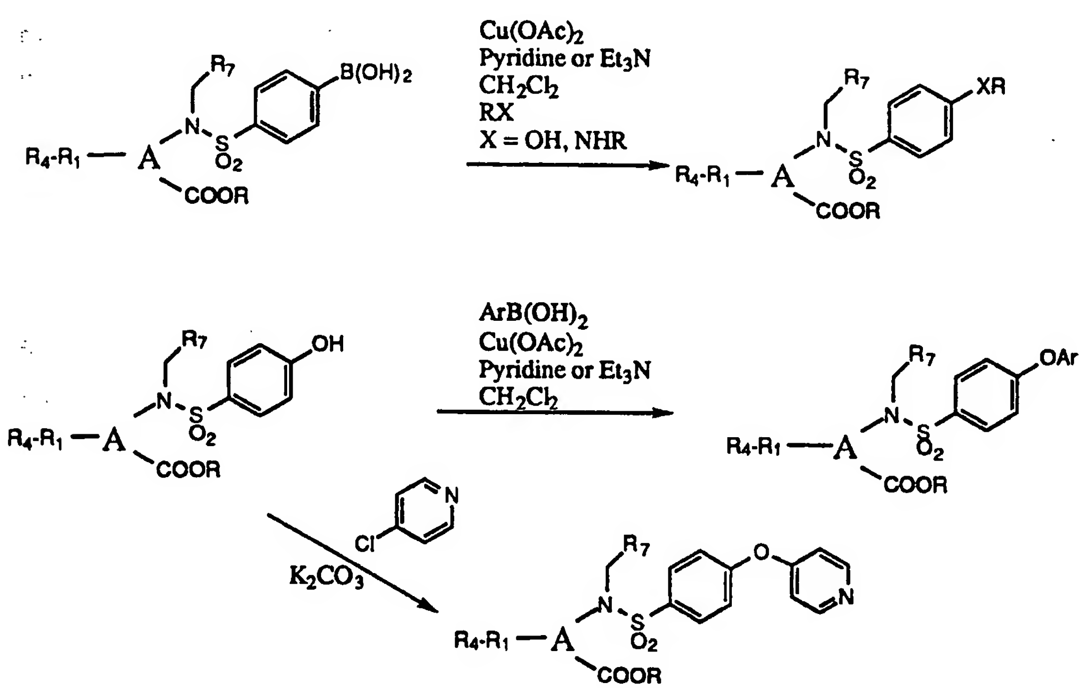
Methods for synthesizing sulfonyl aryl ethers are shown in Schemes VII through IX. In Scheme VII biaryl ethers, or aryl heteroaryl ethers, are synthesized starting from the known sulfonyl chlorides (see for example: Zook SE; Dagnino, R; Deason, ME, Bender, SL; Melnick, MJ WO 97/20824).

Scheme VII.



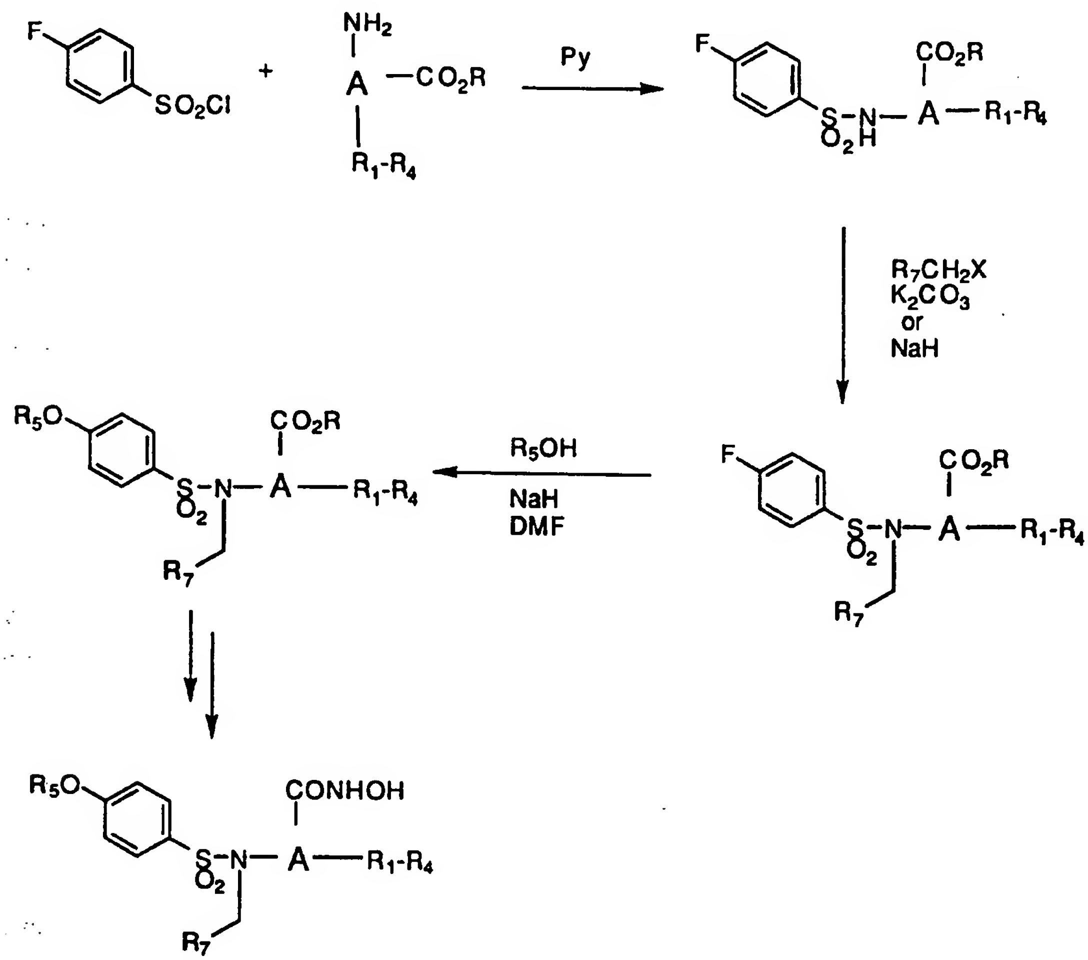
Alternatively, the biaryl ethers may be prepared from the corresponding boronic acids or via the sulfonyl phenols as shown in Scheme VIII.

Scheme VIII.



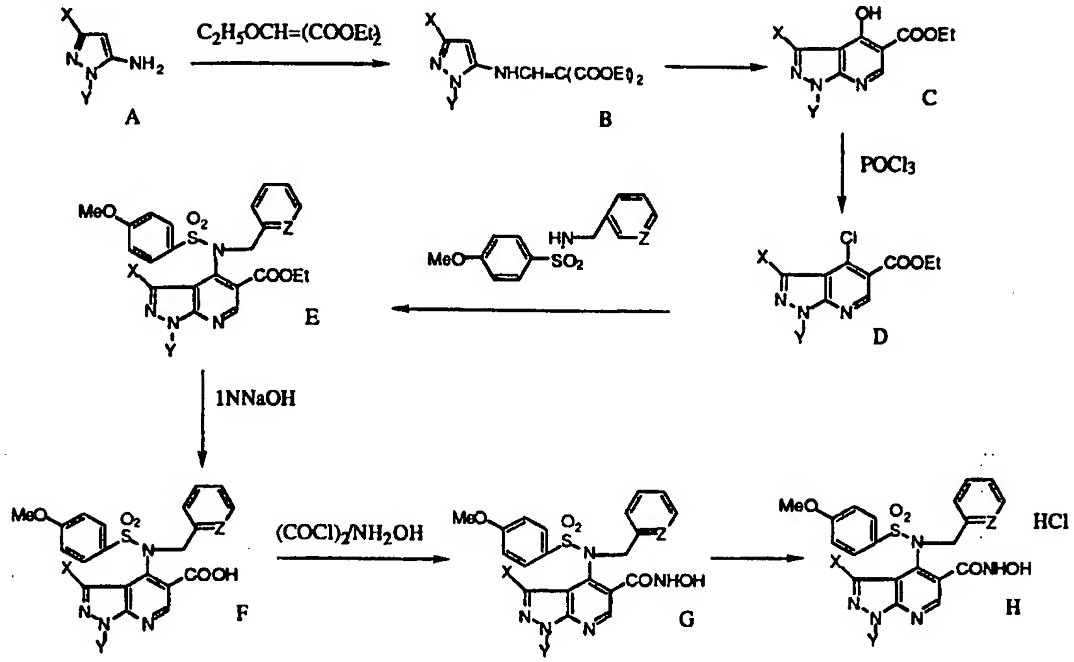
Aryl ethers may also be prepared via displacement of the fluorine from a para-fluorobenzene sulfonamide, as shown in Scheme IX. Aryl or alkyl ethers may be prepared in this manner.

Scheme IX.



Scheme X illusstrates the synthesis of pyrazolopyridines of the invention. Thus, a substituted amino-pyrazole is condensed with ethoxymethylene malonate to provide the pyrazolylamino methylene malonate, B. This compound is converted into the pyrazolopyridine, C, by heating at 240°C. Compound C is then converted into the chloro-ester, D, via reaction with phosphorus oxychloride. Displacement of the chloro substituent with a sulfonamide then gives compound E. Hydrolysis of the ester and conversion of the carboxylate into the hydroxamate then gives compound G.

Scheme X.



The following specific examples are provided to illustrate the preparation of compounds of this invention and are not to be construed as limiting this invention in any way. Other procedures for preparing the compounds of this invention will be apparent to those skilled in the art of organic synthesis. All starting materials, intermediates, and reagents are either commercially available or can be readily prepared following standard literature procedures by one skilled in the art of organic synthesis.

Example 1

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester

To a solution of 1.85g (6.67 mmol) of N-benzyl 4-methoxyphenylsulphonamide in 15mL of DMF was added, in one portion, 0.267g (6.67 mmol) of 60% sodium hydride and the resulting mixture was stirred at room temperature under nitrogen for 15 min. Ethyl 4-chloro-7-trifluoromethyl-3-quinolinecarboxylate (2.02g, 6.67 mmol) was then added to the solution in one portion and the resulting mixture was heated at 85 °C for 24h. The reaction mixture was then cooled to room temperature, poured into a mixture of water (300 mL) and HCl (1N, aqueous, 100 mL) and extracted with ethyl acetate (2x100 mL). The

combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was then chromatographed on silica gel eluting with 15%-50% ethyl acetate/ hexane to give 3.11g (88%) of the desired product. Electrospray Mass Spec 545.1 (M+H).

Example 2

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-8-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester

In the same manner as described in Example 1, 1.012g (3.34 mmol) of ethyl 4-chloro-8-trifluoromethyl-3-quinolinecarboxylate provided 1.509g (83%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 545.1 (M+H).

Example 3

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]- 6-bromo-quinoline-3-carboxylic acid ethyl ester

In the same manner as described in Example 1, 0.848g (2.70 mmol) of ethyl 6-bromo-4-chloro-3-quinolinecarboxylate provided 1.418g (95%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 557.1 (M+H).

Example 4

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]- 7-bromo-quinoline-3-carboxylic acid ethyl ester

In the same manner as described in Example 1, 0.777g (2.47 mmol) of ethyl 7-bromo-4-chloro-3-quinolinecarboxylate provided 1.169g (85%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 557.1 (M+H).

Example 5

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester

In the same manner as described in Example 1, 1.216g (4.02 mmol) of ethyl 4-chloro-6-trifluoromethyl-3-quinolinecarboxylate provided 2.171g (99%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 545.0 (M+H).

Example 6

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid

To a solution of 1.065g (2.00 mmol) of the product from Example 1 in 4mL of methanol/THF (1:1) was added 2mL of 1N sodium hydroxide solution and the resulting mixture was stirred at 25 °C for 18h. The reaction was then acidified with 1N HCl and extracted with ethyl acetate (200 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was triturated with ethyl acetate/hexane (1:9) and filtered to provide 828 mg (82%) of the desired carboxylic acid as a white solid. Electrospray Mass Spec 517.1 (M+H)

Example 7

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-8-trifluoromethyl-quinoline-3-carboxylic acid

In the same manner as described in Example 6, 1.255g (2.64 mmol) of the product from Example 2 provided 0.988g (83%) of the desired quinoline acid as a white solid. Electrospray Mass Spec 517.1 (M+H).

Example 8

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-bromo-quinoline-3-carboxylic acid

In the same manner as described in Example 6, 1.198g (2.16 mmol) of the product from Example 3 provided 0.921g (81%) of the desired quinoline acid as a white solid. Electrospray Mass Spec 529.0 (M+H).

Example 9

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]- 7-bromo-quinoline-3-carboxylic acid

In the same manner as described in Example 6, 0.969g (1.74 mmol) of the product from Example 4 provided 0.804g (87%) of the desired quinoline acid as a white solid. Electrospray Mass Spec 529.0 (M+H).

Example 10

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-trifluoromethyl-quinoline-3-carboxylic acid

In the same manner as described in Example 6, 2.043g (3.75 mmol) of the product from Example 5 provided 1.82g (88%) of the desired quinoline acid as a white solid.

Electrospray Mass Spec 515.0 (M-H).

Example 11

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide

To a solution of 0.636g (1.26 mmol) of the product from Example 6 in 12.5 mL of dichloromethane was added 0.05 mL of DMF followed by 1.26 mL (2.52 mmol) of 2 M oxalyl chloride and the resulting reaction mixture was stirred at room temperature for 1h.

In a separate flask, 2.6 mL (19 mmol) of triethylamine was added to a 0°C mixture of 350 mg (13 mmol) of hydroxylamine hydrochloride in 14 mL of THF and 3.5 mL of water. After this mixture had been stirred for 15min at 0 °C, the acid chloride solution was added to it in one portion and the resulting solution was allowed to warm to room temperature and stirred for another 4h. Water was then added to the reaction flask and 0.488g (75%) product was collected via filtration. Electrospray Mass Spec 532.1 (M+H)

Example 12

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-8-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 11, 0.444g (3.75 mmol) of the product from Example 7 provided 0.143g (31%) of the desired quinoline hydroxamic acid as a cream colored solid. Electrospray Mass Spec 532.1 (M+H).

Example 13

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]- 6-bromo-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 11, 0.527g (1.00 mmol) of the product from Example 8 provided 0.367g (68%) of the desired quinoline hydroxamic acid as a off-white solid. Electrospray Mass Spec 541.9 (M+H).

Example 14

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]- 7-bromo-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 11, 0.527g (1.00 mmol) of the product from Example 9 provided 0.280g (52%) of the desired quinoline hydroxamic acid as a white solid. Electrospray Mass Spec 541.9 (M+H).

Example 15

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 11, 0.527 g (1.06 mmol) of the product from Example 10 provided 0.435g (77%) of the desired quinoline hydroxamic acid as a cream colored solid. Electrospray Mass Spec 532.1 (M+H).

Example 16

4-[(4-Methoxybenzenesulfonyl)-pyridin-3-ylmethylamino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide

Following the procedure of example 1 and substituting N-(3-pyridinylmethyl)-4-methoxybenzenesulfonamide for N-benzyl-4-methoxybenzenesulfonamide, the intermediate 4-[(4-methoxybenzenesulfonyl)-pyridin-3-ylmethylamino]-7-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester is obtained. Following the procedures of example 6 and 11, the title product is obtained. Electrospray Mass Spec 533.0 (M+H).

Example 17

4-[Benzyl-(4-methoxybenzenesulfonyl)-amino]-8-t-butyl-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 1, 1.167g (4.00 mmol) of ethyl 4-chloro-8-butyl-3-quinolinecarboxylate provided 1.413g (66%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 533.3 (M+H).

In the same manner as described in Example 6, 1.065g (2.00 mmol) of the ester provided 0.478g (47%) of the desired quinoline acid as a white solid. Electrospray Mass Spec 503.3 (M-H).

Following the procedures of example, the title compound is obtained from the carboxylic acid. Electrospray Mass Spec. 520.3 (M+H).

Example 18

4-[Benzyl-(4-methoxybenzenesulfonyl)-amino]-8-methyl-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 1, 1.00g (4.00 mmol) of ethyl 4-chloro-8-methyl-3-quinolinecarboxylate provided 0.531g (27%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 491.3 (M+H).

In the same manner as described in Example 6, 0.470g (0.851 mmol) of the ester provided 0.160g (41%) of the desired quinoline acid as a white solid. Electrospray Mass Spec 461.3 (M-H).

Following the procedure of example 11, the title compound is obtained from the carboxylic acid. Electrospray Mass Spec. 478.3 (M+H).

Example 19

4-[Benzyl-(4-methoxybenzenesulfonyl)-amino]- 8-ethyl-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 1, 1.055g (4.00 mmol) of ethyl 4-chloro-8-ethyl-3-quinolinecarboxylate provided 0.670g (33%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 505.3 (M+H).

In the same manner as described in Example 6, 0.615g (1.22 mmol) of the product from Example 7 provided 0.353g (60%) of the desired quinoline acid as a white solid. Electrospray Mass Spec 475.3 (M-H).

Following the procedure of example 11, the title compound is obtained from the carboxylic acid. Electrospray Mass Spec. 492.3 (M+H).

Example 20

4-[Benzyl-(4-methoxybenzenesulfonyl)-amino]-8-(1-methylethyl)-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 1, 1.111g (4.00 mmol) of ethyl 4-chloro-8-isopropyl-3-quinolinecarboxylate provided 0.754g (36%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 519.3 (M+H).

In the same manner as described in Example 6, 0.686g (0.127 mmol) of the ester provided 0.532g (82%) of the desired quinoline acid as a white solid. Electrospray Mass Spec 489.2 (M-H).

In the same manner as described in Example 11, 0.440g (0.897 mmol) of the hydroxamic acid provided 0.270 g (60%) of the desired quinoline hydroxamic acid. Electrospray Mass Spec. 506.3 (M+H).

Example 21

4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]- 8-iodo-quinoline-3-carboxylic acid ethyl ester

In the same manner as described in Example 1 and substituting N-ethyl-4-methoxybenzenesulfonamide for N-benzyl-4-methoxybenzenesulfonamide, 1.076g (5.00 mmol) of ethyl 8-iodo-4-chloro-3-quinolinecarboxylate provided 2.438g (4.51 mmol, 90%) of the desired quinoline ester as a white solid. Electrospray Mass Spec 541.0 (M+H).

Example 22

4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-8-vinyl-quinoline-3-carboxylic acid ethyl ester

The product from example 21 (2.438g, 4.51mmol) in 150 mL DMF was added tributylvinyltin (1.43g, 4.51 mmol), tetrakis(triphenylphosphine)palladium(0) (520mg, 10%), cuprious iodide (171mg, 20%), and 5 mL triethylamine. The mixture was stirred under N2 and heated at 85°C for 18 hours. The it was poured into a mixture (1:1) of 400 mL saturated sodium bicarbonate and saturated amonium chloride and extracted with ethyl acetate (2x200 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated on a rotary evaporator. The residue was column chromatographed using 300 mL silica gel and gradient elution with hexane/ethyl acetate (100~0%). This provided 1.706g (3.88 mmol, 86%) of the desired quinoline ester. Electrospray Mass Spec 441.1 (M+H).

Example 23

4-[Methyl-(4-methoxy-benzenesulfonyl)-amino]-6-phenylethynyl-quinoline-3-carboxylic acid ethyl ester

Combining the procedures of examples 1 and 22, and substituting phenylacetylene for vinyltin, N-ethyl-4-methoxybenzenesulfonamide for N-benzyl-4-methoxybenzenesulfonamide, the intermediate 4-[ethyl-(4-methoxy-benzenesulfonyl)-amino]-6-phenylethynyl-quinoline-3-carboxylic acid ethyl ester is obtained from ethyl -4-chloro-3-quinolinecarboxylate. Electrospray Mass Spec 515.3 (M+H).

Example 24

4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-8-vinyl-quinoline-3-carboxylic acid

In the same manner as described in Example 6, 1.593g (3.62 mmol) of the product from Example 22 provided 1.333g (89%) of the desired quinoline acid as a white solid. Electrospray Mass Spec 411.1 (M-H).

Example 25

4-[Methyl-(4-methoxy-benzenesulfonyl)-amino]-6-phenylethynyl-quinoline-3-carboxylic acid

In the same manner as described in Example 6, the title compound was synthesized from the product of example 23. Electrospray Mass Spec 485.3 (M-H).

Example 26

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-nitro-quinoline-3-carboxylic acid

In the same manner as described in Example 1 and 6, 5.613g (20.0 mmol) ethyl 4-chloro-6-nitro-3-quinolinecarboxylate provided 2.676g (27% for two steps) of the title compound as a white solid. Electrospray Mass Spec 492.3 (M-H).

Example 27

4-[Methyl-(4-methoxy-benzenesulfonyl)-amino]- 8-bromo-quinoline-3-carboxylic acid

Combining the procedures of example 1 and 6, and substituting N-methyl-4-methoxybenzenesulfonamide for N-benzyl-4-methoxybenzenesulfonamide, the intermediate 8-bromo-4-[methyl-(4-methoxy-benzenesulfonyl)-amino]-quinoline-3-carboxylic acid is obtained. Electrospray Mass Spec 449.2 (M-H).

Example 28

4-{Methyl-(4-(pyridin-4-yloxy)-benzenesulfonyl]-amino}-6-iodo-quinoline-3-carboxylic acid

Combining the procedures of example 1 and 6, and substituting N-methyl-4-(pyridin-4-yloxy)-benzenesulfonamide the intermediate 6-iodo-4-{methyl-(4-(pyridin-4-yloxy)-benzenesulfonyl]-amino}-quinoline-3-carboxylic acid is obtained from ethyl 6-iodo-4-chloro-3-quinolinecarboxylate. Electrospray Mass Spec 559.9 (M-H).

Example 29

4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-8-vinyl-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 11, 0.484g (1.17 mmol) of the product from Example 24 provided 0.360g (72%) of the desired quinoline hydroxamic acid. Electrospray Mass Spec. 428.0 (M+H).

Example 30

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-nitro-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 11, 0.825g (1.67 mmol) of the product from Example 26 provided 0.227g (0.446 mmol, 26%) of the desired quinoline hydroxamic acid. Electrospray Mass Spec. 509.0 (M+H).

Example 31

4-[Methyl-(4-methoxy-benzenesulfonyl)-amino]- 8-bromo-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 11, 0.664g (1.47 mmol) of the product from Example 27 provided 0.145g (0.311 mmol, 21%) of the desired quinoline hydroxamic acid. Electrospray Mass Spec. 468.0 (M+H).

Example 32

4-{Methyl-[4-(pyridin-4-yloxy)-benzenesulfonyl]-amino}-6-iodo-quinoline-3-carboxylic acid hydroxyamide

To a 0 °C solution of of 4.5 mL oxalyl chloride (0.90 mmol, 2M in dichloromethane) was added dropwise 0.69 mL of DMF. The resulting solid was kept at 0 °C for another 15 minutes and followed by addition of 2.50g (4.46 mmol) of the product from Example 28 in 50 mL DMF. The mixture was stirred for 1 hour at room temperature and then kept at 0 °C for an additional 15 minutes. An aqueous solution of hydroxylamine (5mL, 50%) was then added all at once to the above solution and the mixture was stirred at room temperature for 3 hours. The mixture was next poured into 300mL water and extracted with dichloromethane (4x100mL). The combined organic layers were washed with brine (300mL) and dried over magnesium sulfate. After filtration and concentration on a rotary evaporator the residue was column chromatographed using gradient methanol in ethyl acetate (20~100%) and it provided 1.36g (2.36mmol, 53%) of the desired quinoline hydroxamic acid. Electrospray Mass Spec. 576.9 (M+H).

Example 33

4-{Methyl-(4-(pyridin-4-yloxy)-benzenesulfonyl]-amino}-6-iodo-quinoline-3-carboxylic acid hydroxyamide hydrochloride

The product from example 32 (0.952 g, 1.65 mmol) was dissolved in 100 mL methanol in a Parr reactor. Degussa catalyst (10% Pd-C, 200mg) was next added under N2. The mixture was then hydrogenated (35 psi) for one hour at room temperature. The mixture was then filtered through a pad of celite and concentrated on a rotary evaporator. The residue was chromatographed with methanol and ethyl acetate (5~35%). The product obtained was next dissolved in methanol and anhydrous hydrochloride was bubbled into the solution for 5 minutes. Removal of the solvent through rotary evaporation and vacuum pump gave 0.707g (1.45 mmol, 88%) product. Electrospray Mass Spec. 450.9 (M+H).

Example 34

4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-6-phenylethynyl-quinoline-3-carboxylic acid hydroxyamide

In the same manner as described in Example 11, 2.432g (5.00 mmol) of the product from Example 25 provided 2.159g (86%) of the desired quinoline hydroxamic acid. Electrospray Mass Spec. 502.1 (M+H).

Example 35

4-[Methyl-(4-methoxy-benzenesulfonyl)-amino]-6-phenylethyl-quinoline-3-carboxylic acid hydroxyamide

The product from example 34 (0.82g, 1.64 mmol) was dissolved in 50 mL methanol in a Parr reactor. Degussa Catalyst (10% Pd-C, 200mg) was next added under N2. The mixture was hydrogenated (45 psi) for one hour at room temperature. The mixture was then filtered through a pad of celite and concentrated on a rotary evaporator. This gave 0.76g (1.50 mmol, 92%) product. Electrospray Mass Spec. 506.0 (M+H).

Example 36

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]- 8-methoxy-quinoline-3-carboxylic acid hydroxyamide

Following the procedure of Example 16 and starting with ethyl 4-chloro-8-methoxy-3-quinolinecarboxylate the title compound was obtained as a yellow powder. Electrospray Mass Spec. 495.3 (M+H).

Example 37

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]- 8-bromo-quinoline-3-carboxylic acid hydroxyamide

Following the procedure of Example 16 and starting with ethyl 4-chloro-8-bromo-3-quinolinecarboxylate the title compound was obtained as a white powder. Electrospray Mass Spec. 543.2 (M+H).

Example 38

4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl amino]-8-Benzyl-quinoline-3-carboxylic acid hydroxyamide

Following the procedure of Example 16 and starting with ethyl 4-chloro-8-benzyl-3-quinolinecarboxylate the title compound was obtained as a beige powder. Electrospray Mass Spec. 555.4 (M+H).

Example 39

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]- 8-iodo-quinoline-3-carboxylic acid hydroxyamide

Following the procedure of Example 16 and starting with ethyl 4-chloro-8-iodo-3-quinolinecarboxylate the title compound was obtained as a yellow powder. Electrospray Mass Spec. 590.8 (M+H).

Example 40

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-8-phenyl-quinoline-3-carboxylic acid hydroxyamide

Following the procedure of Example 16 and starting with ethyl 4-chloro-8-phenyl-3-quinolinecarboxylate the title compound was obtained as a beige powder. Electrospray Mass Spec. 541.4 (M+H).

Example 41

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-8-thiophen-2-yl-quinoline-3-carboxylic acid hydroxyamide

Combining the procedures of Examples 22, 6 and 11 and starting with4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]- 8-bromo-quinoline-3-carboxylic acid ethyl ester and 2-tributylstannylthiophene the title compound was obtained as a yellow powder. Electrospray Mass Spec. 545.0 (M+H).

Example 42

4-[(Biphenyl-4-sulfonyl)-pyridin-3-ylmethyl-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide

Following the procedure of Example 1 and substituting N-(3-pyridinylmethyl)-4-bromobenzenesulfonamide for N-benzyl-4-methoxybenzenesulfonamide, the intermediate 4-[(4-bromobenzenesulfonyl)-pyridin-3-ylmethylamino]-7-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester is obtained.

To 8.5 mL of degassed ethylene glycol dimethyl ether, was added 500 mg (0.85 mmol) of the ester, 110 mg (0.93 mmol) of phenylboronic acid, 80 mg (0.07 mmol) of tetrakis(triphenylphosphine)palladium and 1.1 ml (2.2 mmol) of 2M aqueous Na_2CO_3 and the mixture ws heated to reflux under nitrogen for 36 hr. The reaction was cooled to room temperature, diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give 4-[(biphenyl-4-sulfonyl)-pyridin-3-ylmethyl-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid ethyl ester.

This ester was converted to the title compound (off-white powder) as described in Examples 6 and 11. Electrospray Mass Spec. 579.1 (M+H).

Example 43

4-[(Octane-1-sulfonyl)-pyridin-3-ylmethyl-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide

Combining the procedures of Examples 1, 6 and 11 and substituting N-(3-pyridinylmethyl)-octanesulfonamide for N-benzyl-4-methoxybenzenesulfonamide the title compound was obtained as a yellow solid. Electrospray Mass Spec. 539.5 (M+H).

Example 44

4-[Pyridin-3-ylmethyl-(toluene-4-sulfonyl)-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide

Combining the procedures of Examples 1, 6 and 11 and substituting N-(3-pyridinylmethyl)-toluenesulfonamide for N-benzyl-4-methoxybenzenesulfonamide the title compound was obtained as a white powder. Electrospray Mass Spec. 517.1 (M+H).

Example 45

Diethyl{[(1-phenyl-5-pyrazolyl) amino] methylene} malonate

A mixture of 15.9 g. (0.10 mole) of 1-phenyl-5-aminopyrazole and 21.6 g. (0.10 mole) of diethyl ethoxymethylenemalonate was heated at 115-120° in an oil bath for 2 hours. After cooling, the crystalline mass was recrystallized from hot hexane containing 1% of ethanol. Cooling to room temperature and filtering gave 24.8 g. (75%) of off-white crystals, m.p. 96-97°C.

Example 46

Ethyl 4-hydroxy-1-phenyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylate

A mixture of 18.1 g. (0.055 mole) of diethyl {[(1-phenyl-5-pyrazolyl)amino]methylene} malonate and 150 ml of diethyl phthalate was heated at 240-250° for 1 hour. The mixture was chilled and diluted with hexane. Chilling and filtering gave crystals which were washed with hexane and with hexane-ethanol (1:1) to give 11 g. (70%) of off white crystals m.p. 149-150°C. From a similar small scale run 1.75 g. was recrystallized from 110 ml. of ethanol to give 1.58 g. of off white crystals, m.p. 149-150° C.

Example 47

Ethyl 4-chloro-1-phenyl-1H-pyrazolo [3,4-b]pyridine-5-carboxylate

A mixture of 5.76 g (20.33 mmol) of ethyl 4-hydroxy-1-phenyl-1H-pyrazolo[3,4-b] pyridine-5- carboxylate and 15.58 g of phosphorus oxychloride was refluxed 1.5 hr, chilled and poured slowly onto crushed ice. The mixture was filtered and the solid washed with ice-water and dried to give 6.0 g of solid, m.p. 89-91° C.

Example 48

Ethyl 4-chloro-1,3-dimethyl-1H-pyrazolo [3,4-b]pyridine-5-carboxylate

Following the procedures of Examples 45, 46 and 47, starting from 1,3-dimethyl-5-aminopyrazole, the chloro-ester is prepared. m.p. 89-90° C.

Example 49

Ethyl 4-[benzyl-(4-methoxybenzenesulfonyl)amino]- 1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylate

To a solution of 1.16 g (4.2 mmol) of benzyl-(4-methoxybenzenesulfonyl)amine in 6 ml of anhydrous 1-methyl-2-pyrrolidinone was added 0.168 g (4.2 mmol) of sodium hydride (60% in oil) and the mixture stirred at room temperature until gas evolution ceased. The preceding mixture was added to mixture of 1.01 g (4 mmol) of ethyl 4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridine -5-carboxylate in 2 ml of 1-methyl -2-pyrrolidinone.

The mixture was heated in an oil bath at 50°C overnight and then was heated in an oil bath at 100° C for 1.5 days. The mixture was poured into 800 ml of water and extracted with ethyl acetate. The extract was washed with water, 2N citric acid, water, brine and dried (Na_2SO_4). The solvent was removed and the residue chromatographed on silica gel with hexane-ethyl acetate (2:1) as eluent to give 0.64 g of product as a solid, mp 170-172°. From a larger scale run of 5.07 g (0.02 mmol) of ethyl 4-chloro-1,3-dimethylpyrazolo [3,4-b]pyridine-5-carboxylate and 8.0 g (0.0289 mmol) of benzyl -(4-methoxybenzenesulfonyl) amine (as sodium anion) in 30 ml of 1-methyl-2-pyrrolidinone heated at 90° C for 3 days there was obtained 3.65 g of product.

Example 50

4-[Benzyl-(4-methoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylic acid.

A mixture of 0.48 g (0.97 mmol) of ethyl 4-[benzyl-(4-methoxybenzenesulfonyl) amino] -1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate and 0.29 ml of 10N NaOH in 4 ml of tetrahydrofuran-methanol (1:1) was heated in an oil bath at 70° C for 2 hours and the solvent removed under vacuum. The residue was dissolved in 20 ml of H_2O

and the solution extracted with 10 ml of diethyl ether. To the aqucous layer was added 2N citric acid (pH 4-5) and the precipitated solid filtered and washed with H_2O to give a white solid which was dried under vacuum overnight to give crystals, mp 165-167°C.

Example 51

4-[Benzyl-(4-methoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, potassium salt.

A mixture of 3.60 g (7.28 mmol) of ethyl 4-[benzyl-(4-methoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate and 0.44 g (7.84 mmol) of potassium hydroxide (pellet) in 15 ml of methanol- water (1:1) was refluxed overnight. An additional 40 mg of potassium hydroxide was added and the mixture refluxed for 4 hours (all the solid dissolved). The solvent was removed under vacuum and toluene added and removed under vacuum. The residue was triturated with ethyl acetate, filtered and the solid washed with ethyl acetate to give 3.8 g of product as a white solid.

Example 52

4-[Benzyl-(4-methoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide

To a chilled solution of 1 ml (2 mmol) of oxalyl chloride in 8 ml of CH_2 Cl_2 was added dropwise 0.154 ml (2 mmol) of N, N-dimethylformamide and the solution stirred 15 min. To the preceding chilled solution was added 0.504 g (1 mmol) of 4-[benzyl-(4-methoxybenzenesulfonyl) amino]-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, potassium salt and the mixture stirred under nitrogen for 2 hrs at room temperature (solution A). A solution of 0.278 g (4 mmol) of hydroxylamine hydrochloride and 0.834 ml (6 mmol) of triethylamine in 5 ml of H_2O-tetrahydrofuran (1:4) was chilled at in an ice bath for 20 min. and to this solution was added dropwise the chilled solution of A. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was removed and the residue extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with 2N citric acid, H_2O, 1N $NaHCO_3$, H_2O, brine and dried (Na_2SO_4). The solvent was removed to give 0.53g of solid. Trituration with ethyl acetate gave 0.278 g of white solid, mp 184-186°C.

Example 53

Ethyl 4-[(4-methoxybenzenesulfonyl)pyridin -3-ylmethylamino] -1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate

To a solution of 1.39 g (5 mmol) of (4-methoxybenzenesulfonyl)(3-pyridinylmethyl) amine in 4 ml of anhydrous 1-methyl-2-pyrrolidinone was added 0.2 g (5 mmol) of sodium hydride (60% in oil) and the mixture stirred at room temperature until gas evolution ceased. To this mixture was added 1.15 g (4.54 mmol) of ethyl 4-chloro-1,3-dimethylpyrazolo[3,4-b]pyridine-5-carboxylate and 2 ml of anhydrous 1-methyl-2-pyrrolidinone. The mixture was stirred in a sealed tube under nitrogen in an oil bath at 90°C for 3 days. The mixture was cooled, poured into water and extracted with ethyl acetate. The extract was washed with H_20, brine and dried (Na_2SO_4). The solution was filtered through a thin pad of hydrous magnesuim silicate and the filter pad washed with ethyl acetate. The filtrate was concentrated to dryness under vacuum to give 1.3 g of solid. Chromatography on silica gel with ethyl acetate as solvent gave 0.35 g of product as a solid, mp 152-154°C.

Example 54

4-[(4-Methoxybenzenesulfonyl) pyridin -3-ylmethylamino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid

A mixture of 1.34 g (2.7 mmol) of ethyl 4-[(4-methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-5-carboxylate, 2.97 ml of 1N potassium hydroxide in 7.8 ml of ethanol and 4.83 ml of water was refluxed for 20 hr. Another 0.54 ml of 1N potassium hydroxide was added and the mixture refluxed 4 hrs. The solvent was removed under vacuum and toluene added and removed under vacuum. The residue was dissolved in water (20ml) and extracted with ethyl acetate. The aqueous layer was acidified with 2 N citric acid and the precipitated solid filtered off and washed with water. The solid was dried under vacuum to give 0.98 g of solid, mp 256-258°C.

Example 55

4-[(4-Methoxybenzenesulfonyl) pyridin -3-ylmethylamino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, potassium salt

A mixture of 0.34 g (0.68 mmol) of ethyl 4-[(4-methoxybenzenesulfonyl) pyridin-3-ylmethylamino]-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate and 0.748 ml of 1 N potassium hydroxide in 4 ml of ethanol- water (1:1) was refluxed for 24 hr. The solvent was removed under vacuum and to the residue was added toluene. The solvent was

removed under vacuum to remove the water and the residue triturated with ethyl acetate to give the product as a solid, mp 160-167° C.

Example 60

4-[(4-Methoxybenzenesulfonyl)pyridin -3-ylmethylamino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide

A 1.5 g (2.459 mmol) sample of 4-[(4-methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid was dissolved in 2.70 ml of 1N KOH. The water was removed by repeated additions and removal of toluene under vacuum to give 1.34 g of solid (potassium salt of the acid). A solution of 2.65 ml (5.3 mmol) of oxalyl chloride was cooled in an ice bath and 0.389 ml of N,N-dimethylformamide added dropwise. After 5 min. the 1.34 g of the previously prepared potassium salt was added and the mixture stirred for 10 min. in an ice bath and then allowed to warm to room temperature (mixture A). A mixture of 0.737 g (10.6 mmol) of hydroxylamine hydrochloride and 2.21 ml (15.9 mmol) of triethyamine in 9.39 ml of tetrahydrofuran and 2.45 ml of water was chilled in an ice bath (mixture B). The mixture A was chilled in an ice bath and added to the chilled and stirred mixture B. The mixture of A and B was stirred at 0°C for 10 min and allowed to warm to room temperature and stir overnight. The solvent was removed under vacuum and the residue diluted with H_2O, acidified with 2 N citric acid and extracted with two 30-ml portions of CH_2Cl_2. The aqueous layer was neutrallized with solid $NaHCO_3$ to bring the pH to 7. The solid which precipitated was filtered and washed with H_2O to give 0.610 g of product as a solid, mp. 202-204°C. The CH_2Cl_2 extract was extracted with 2 N citric acid and the aqueous layer neutrallized with solid $NaHCO_3$. The precipitated solid was filtered off and washed with water to give 0.226 g of product, mp 196-198°C. (mass spectrum (ES) 483.5 (M+1).

Example 61

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide hydrochloride

To a solution of 0.610g (1.265 mmol) of 4-[(4-methoxybenenzenesulfonyl)pyridin -3-ylmethylamino]-1,3-dimethyl-5-carboxylic acid, hydroxyamide in 40 ml of CH_2Cl_2-methanol (1:1) cooled to 10°C was added dropwise 1.51 ml of 1M hydrogen chloride in diethyl ether. The mixture was stirred at 10°C for 10 min. and allowed to warm to room temperature for 1 hr. The solvent was removed under vacuum and toluene (2ml) added

twice and removed under vacuum after each addition. The residual solid was dried under vacuum to give 0.641 g of product as a solid, m.p. 170°-174°C.

Example 62

4-[Benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-1H-pyrazolo[3,4-b] pyridine -5-carboxylic acid, hydroxyamide

Following the procedure of Example 49, the product of Example 47 is reacted with benzyl-(4-methoxybenzenesulfonyl)amine and sodium hydride to provide ethyl 4-[benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. m.p. 124°-126°C.

Following the procedure of Example 50, the above ester is hydrolyzed to provide 4-[benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid. m.p. 108°-110°C.

Following the procedure of Example 52, the carboxylic acid is converted into the corresponding hydroxamic acid, 4-[benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-1H-pyrazolo[3,4-b] pyridine -5-carboxylic acid, hydroxyamide. m.p. 152°-154°C.

Example 63

4-[(4-Methoxybenzenesulfonyl)pyridin -3-ylmethylamino] -1-phenyl- 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide

Following the procedure of Example 53, the product of Example 47 is reacted with (4-methoxybenzenesulfonyl) (3-pyridinylmethyl) amine and sodium hydride to provide ethyl 4-[(4-methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. m.p. 89°-91°C.

Following the procedure of Example 54, the above ester is hydrolyzed to provide 4-[(4-methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-phenyl-1H-pyrazolo[3,4b] pyridine-5-carboxylic acid. m.p. 136°-138°C.

Following the procedure of Example 60, the carboxylic acid is converted into the corresponding hydroxamic acid, 4-[(4-methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-phenyl- 1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide. m.p. 114°C(dec).

Example 64

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide, hydrochloride

Following the procedure of Example 61, the product of Example 63 is converted into the corresponding hydrochloride salt. m.p. 161°C(dec).

Example 65

Ethyl 4-chloro-1-phenyl-3-methyl-1H-pyrazolo [3,4-b]pyridine-5-carboxylate

Following the procedure of Example 45, starting with 1-phenyl-3-methyl-5-aminopyrazole, diethyl{[(1-phenyl-3-methyl-5-pyrazolyl)amino]methylene}malonate is obtained. m.p. 70°-72°C.

Following the procedure of Example 46, the methylene malonate is converted into ethyl 4-hydroxy-1-phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. m.p. 132°-134°C.

Following the procedure of Example 47, the hydroxy-ester is converted into the chloro-ester, ethyl-4-chloro-1-phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. m.p. 108°-110°C.

Example 66

4-[Benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-3-methyl-1H-pyrazolo[3,4b] pyridine-5-carboxylic acid, hydroxyamide

Following the procedure of Example 49, the product of Example 65 is reacted with benzyl-(4-methoxybenzenesulfonyl)amine and sodium hydride to provide ethyl 4-[benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. m.p. 164°-166°C.

Following the procedure of Example 50, the above ester is hydrolyzed to provide 4-[benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-3-methyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid. m.p. 246°-248°C.

Following the procedure of Example 52, the carboxylic acid is converted into the corresponding hydroxamic acid, 4-[benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide. m.p. 207°-210°C.

Example 67

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide

Following the procedure of Example 53, the product of Example 65 is reacted with (4-methoxybenzenesulfonyl) (3-pyridinylmethyl) amine and sodium hydride to provide ethyl-4-[(4-methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylate. m.p. 148°-150°C.

Following the procedure of Example 54, the above ester is hydrolyzed to provide 4-[(4-methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid. m.p. 235°-236°C.

Following the procedure of Example 60, the carboxylic acid is converted into the corresponding hydroxamic acid, 4-[(4-methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide. m.p. 192°-194°C.

Example 68

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide, hydrochloride

Following the procedure of Example 61, the product of Example 67 is converted into the corresponding hydrochloride salt. m.p. 225°-226°C.

Example 69

4-[(4-Methoxybenzenesulfonyl)pyridin-2-ylmethyl amino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 70

4-[(4-Methoxybenzenesulfonyl)pyridin-4-ylmethylamino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 71

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino] -1-isopropyl - 1H-pyrazolo[3,4-b]pyridin -5-carboxylic acid, hydroxyamide.

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 72

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino] -1-benzyl-1H-pyrazolo[3,4-b] pyridin -5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 73

4-[(4-Methoxybenzenesulfonyl)amino] -1-benzyl -3-methyl -1H-pyrazolo[3,4-b] pyridine -5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 74

4-[(4-Methoxybenzenesulfonyl) 2-thienylmethylamino] -1, 3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 75

4-[(4-Methoxybenzenesulfonyl) -3-thienylmethylamino] -1, 3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 76

4-[(4-Methoxybenzenesulfonyl) pyridin-3-ylmethylamino] -1- (2,4-dimethoxyphenyl) - 3-methyl- 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 77

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino] -1-(2-methoxyphenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 78

4-{Methyl-[4-(4-pyridinyloxy)benzenesulfonyl]amino}-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 79

4-{Methyl-[4-(phenoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 80

4-[Methyl-(4-methoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 81

4-[Methyl-(4-propyloxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 82

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-methyl-3-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 83

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-ethyl-3-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 84

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-tert-butyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Example 85

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-methyl-3-tert-butyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide

Following procedures described in Examples 45-68 for the preparation of the (substituted-4-amino)1,3-dimethyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamides, the title compound may be prepared.

Pharmacology

Procedures for Measuring MMP-1, MMP-9, and MMP-13 Inhibition

These assays are based on the cleavage of a thiopeptide substrates such as Ac-Pro-Leu-Gly(2-mercapto-4-methyl-pentanoyl)-Leu-Gly-OEt by the matrix metalloproteinases MMP-1, MMP-13 (collagenases) or MMP-9 (gelatinase), which results in the release of a substrate product that reacts colorimetrically with DTNB (5,5'-dithiobis(2-nitro-benzoic acid)). The enzyme activity is measured by the rate of the color increase. The thiopeptide substrate is made up fresh as a 20 mM stock in 100% DMSO and the DTNB is dissolved in 100% DMSO as a 100 mM stock and stored in the dark at room temperature. Both the substrate and DTNB are diluted together to 1 mM with substrate buffer (50 mM HEPES pH 7.5, 5 mM $CaCl_2$) before use. The stock of enzyme is diluted with assay buffer (50 mM HEPES, pH 7.5, 5 mM $CaCl_2$, 0.02% Brij) to the desired final concentration. The assay buffer, enzyme, vehicle or inhibitor, and DTNB/substrate are added in this order to a 96 well plate (total reaction volume of 200 µl) and the increase in color is monitored spectrophotometrically for 5 minutes at 405 nm on a plate reader and the increase in color over time is plotted as a linear line.

Alternatively, a fluorescent peptide substrate is used. In this assay, the peptide substrate contains a fluorescent group and a quenching group. Upon cleavage of the substrate by an MMP, the fluorescence that is generated is quantitated on the fluorescence plate reader. The assay is run in HCBC assay buffer (50mM HEPES, pH 7.0, 5 mM Ca^{+2}, 0.02% Brij, 0.5% Cysteine), with human recombinant MMP-1, MMP-9, or MMP-13. The substrate is dissolved in methanol and stored frozen in 1 mM aliquots. For the assay, substrate and enzymes are diluted in HCBC buffer to the desired concentrations. Compounds are added to the 96 well plate containing enzyme and the reaction is started by the addition of substrate. The reaction is read (excitation 340 nm, emission 444 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line.

For either the thiopeptide or fluorescent peptide assays, the slope of the line is calculated and represents the reaction rate. The linearity of the reaction rate is confirmed (r^2 >0.85). The mean (x±sem) of the control rate is calculated and compared for statistical significance ($p<0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generated using multiple doses of drug and IC_{50} values with 95% CI are estimated using linear regression.

In vivo MMP Inhibition

A 2 cm piece of dialysis tubing (molecular weight cut-off 12-14,000, 10 mm flat width) containing matrix metalloproteinase enzyme (stromelysin, collagenase or gelatinase

in 0.5 mL of buffer) is implanted either ip or sc (in the back) of a rat (Sprague-Dawley, 150-200g) or mouse (CD-1, 25-50g) under anesthesia. Drugs are administered PO, IP, SC or IV through a canula in the jugular vein. Drugs are administered in a dose volume of 0.1 to 0.25 mL/animal. Contents of the dialysis tubing is collected and enzyme activity assayed.

Enzyme reaction rates for each dialysis tube are calculated. Tubes from at least 3 different animals are used to calculate the mean± sem. Statistical significance ($p<0.05$) of vehicle-treated animals versus drug-treated animals is determined by analysis of variance. (*Agents and Actions* 21: 331, 1987).

Procedure for Measuring TACE Inhibition

Using 96-well black microtiter plates, each well receives a solution composed of 10 µL TACE (Immunex, final concentration 1µg/mL), 70µL Tris buffer, pH 7.4 containing 10% glycerol (final concentration 10 mM), and 10 µL of test compound solution in DMSO (final concentration 1µM, DMSO concentration <1%) and incubated for 10 minutes at room temperature. The reaction is initiated by addition of a fluorescent peptidyl substrate (final concentration 100 µM) to each well and then shaking on a shaker for 5 sec.

The reaction is read (excitation 340 nm, emission 420 nm) for 10 min. and the increase in fluorescence over time is plotted as a linear line. The slope of the line is calculated and represents the reaction rate.

The linearity of the reaction rate is confirmed ($r^2 >0.85$). The mean (x±sem) of the control rate is calculated and compared for statistical significance ($p<0.05$) with drug-treated rates using Dunnett's multiple comparison test. Dose-response relationships can be generate using multiple doses of drug and IC_{50} values with 95% CI are estimated using linear regression.

Results of the above in-vitro and in-vivo matrix metalloproteinase inhibition and TACE inhibition pharmacological assays are given in Table I below.

Table I. Inhibition of MMP and TACE

Example	MMP-1[1]	MMP-9[1]	MMP-13[1]	TACE[1]	in-vivo MMP[2]
11	172	11	7	>1000	
12	933	2	1	190	
13	82	15	9	3%	
14	108	8	6	24%	
15	139	25	12	7%	
16	99	6	3	36%	64%(100)
17	3100	8	16	401	
18	152		26	627	
19	194	2	4	314	
20	344	6	9	589	
29	200	5	4		
30	22	11	467	47	
31	225	2	2	80	
32	456	1	1	24	
33	1012	1	1		
34	301	9	12	20	
35	234	4	5	49	
36	46	2	1	226	81%(50)
37	65	2	1	124	
38	100	4	3	336	
39	75	2	2	53	
40	151	3	4	120	
41	136	2	2	161	65%(50)
42	5200	874	37	16%	
43	43%	71%	63%	20%	
44	65%	59%	73%	5%	
52	45	2.4	1.4	236	
60	39	2.9	2.5	160	
61	36	2.3	2.3	214	
62	1236	5.7	23	46%	
63	721	6.8	23		
64	913	5.5	19		

1. IC_{50} nM or % inhibition at 1 μM concentration

2. % inhibition (dose, mg/kg), p.o. vs MMP-13

Pharmaceutical Composition

Compounds of this invention may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such a solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferable sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives, and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

The compounds of this invention may be administered rectally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a

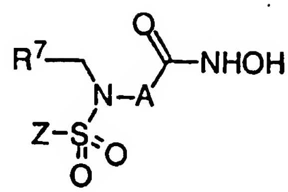
transdermal patch containing the active compound and a carrier that is inert to the active compound, is non-toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semi-solid emulsions of either the oil in water or water in oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage to be used in the treatment of a specific patient suffering a MMP or TACE dependent condition must be subjectively determined by the attending physician. The variables involved include the severity of the dysfunction, and the size, age, and response pattern of the patient. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached. Precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated and standard medical principles.

Preferably the pharmaceutical composition is in unit dosage form, e.g., as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage form can be packaged compositions, for example packed powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

What is claimed:

1. A compound having the formula:



where the hydroxamic acid moiety and the sulfonamido moiety are bonded to adjacent carbons of the heteroaryl ring of group A where:

A is a 5-6 membered heteroaryl having from 1 to 2 heteroatoms independently selected from N, O, and S, and substituted by R^1 and R^2 on adjacent atoms wherein R^1 and R^2 together with the carbons to which they are attached form a fused phenyl ring or a 5-6 membered heteroaryl ring having from 1 to 3 heteroatoms selected independently from N, O and S, wherein either ring can be substituted by one or more substituents selected from R^4;

Z is aryl, heteroaryl, or heteroaryl fused to a phenyl,

where aryl is phenyl or naphthyl optionally substituted by R^1, R^2, R^3 and R^4;

heteroaryl is a 5-6 membered heteroaromatic ring having from 1 to 3 heteroatoms independently selected from N, O, and S, and optionally substituted by R^1, R^2, R^3 and R^4;

and when heteroaryl is fused to phenyl, either or both of the rings can be optionally substituted by R^1, R^2, R^3 and R^4;

R^1, R^2, R^3 and R^4 are independently -H, -COR^5, -F,-Br, -Cl, -I, -C(O)NR^{5}OR^6,-CN, -OR^5,-C_1-C_4-perfluoroalkyl, -S(O)$_x$R^5 where x is 0-2, -OPO(OR^5)OR^6, -PO(OR$_6$)R$_5$, -OC(O)NR^{5}R^6, -COOR^5, -CONR^{5}R^6, -SO$_3$H, -NR^{5}R^6, -NR^{5}COR^6, -NR^{5}COOR^6, -SO$_2$NR^{5}R^6, -NO$_2$, -N(R^5)SO$_2$R^6, -NR^{5}CONR^{5}R^6, -NR^{5}C(=NR^6)NR^{5}R^6, 3–6 membered cycloheteroalkyl having one to three heteroatoms independently selected from N, O, and S and optionally having 1 or 2 double bonds and optionally substituted by one to three groups each selected independently from R^5; -aryl or heteroaryl as defined above, -SO$_2$NHCOR^{5}or -CONHSO$_2$R^5 where R^5 is not H;

-tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR^5R^6$ or straight chain or branched $-C_1-C_6$ alkyl, $-C_2-C_6$-alkenyl, or $-C_2-C_6$-alkynyl, or $-C_3-C_6$-cycloalkyl optionally having 1 or 2 double bonds each optionally substituted with $-COR^5$, -CN, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl,$-OR^5$, $-C_1-C_4$-perfluoroalkyl, $-S(O)_xR^5$ where x is 0-2, $-OC(O)NR^5R^6$, $-COOR^5$, $-CONR^5R^6$, $-SO_3H$, $-NR^5R^6$,$-NR^5COR^6$, $-NR^5COOR^6$, -$SO_2NR^5R^6$, $-NO_2$, $-N(R^5)SO_2R^6$, $-NR^5CONR^5R^6$, $-C_3-C_6$ cycloalkyl as defined above, 3-6 membered cycloheteroalkyl as defined above, aryl or heteroaryl as defined above, $-SO_2NHCOR^5$ or$-CONHSO_2R^5$ where R^5 is not hydrogen, $-PO(OR^5)OR^6$, -$PO(OR^6)R^5$, -tetrazol-5-yl, $-C(O)NR^5OR^6$, -$NR^5C(=NR^6)NR^5R^6$,$-SO_2NHCONR^5R^6$ or $-SO_2NHCN$;

R^5 and R^6 are independently defined as H, aryl and heteroaryl as defined above, $-C_3-C_6$-cycloalkyl as defined above, $-C_3-C_6$-cycloheteroalkyl as defined above, $-C_1-C_4$-perfluoroalkyl, or straight chain or branched $-C_1-C_6$ alkyl, $-C_2-C_6$-alkenyl, or $-C_2-C_6$-alkynyl each optionally substituted with -OH, $-COR^8$, -CN, $-C(O)NR^8OR^9$, $-C_2-C_6$-alkenyl, $-C_2-C_6$-alkynyl, $-OR^8$, $-C_1-C_4$-perfluoroalkyl, $-S(O)_xR^8$ where x is 0–2, $-OPO(OR^8)OR^9$, $-PO(OR^8)R^9$, $-OC(O)NR^8R^9$, $-COOR^8$, - $-CONR^8R^9$, $-SO_3H$, $-NR^8R^9$,$-NCOR^8R^9$, $-NR^8COOR^9$, $-SO_2NR^8R^9$, $-NO_2$, $-N(R^8)SO_2R^9$, $-NR^8CONR^8R^9$, $-C_3-C_6$ cycloalkyl as defined above, $-C_3-C_6$- cycloheteroalkyl as defined above, -aryl or heteroaryl as defined above, $-SO_2NHCOR^8$ or $-CONHSO_2R^8$ where R^8 is not hydrogen, -tetrazol-5-yl, - $-NR^8C(=NR^9)NR^8R^9$, $-SO_2NHCONR^8R^9$, or $-SO_2NHCN$;

R^7 is hydrogen, straight chain or branched $-C_1-C_6$-alkyl, $-C_2-C_6$-alkenyl, or $-C_2-C_6$-alkynyl each optionally substituted with -OH, $-COR^5$, -CN, $-C_2-C_6$-alkenyl, $-C_2-C_6$-alkynyl, $-OR^5$, $-C_1-C_4$-perfluoroalkyl, $-S(O)_xR^5$ where x is 0-2, $-OPO(OR^5)OR^6$, $-PO(OR^5)R^6$, $-OC(O)NR^5R^6$, -$COOR^5$, $-CONR^5R^6$, $-SO_3H$, $-NR^5R^6$,$-NR^5COR^6$, $-NR^5COOR^6$, -$SO_2NR^5R^6$, $-NO_2$, $-N(R^5)SO_2R^6$, $-NR^5CONR^5R^6$, $-C_3-C_6$ cycloalkyl as defined above, $-C_3-C_6$-cycloheteroalkyl as defined above, -aryl or heteroaryl as defined above, $-SO_2NHCOR^5$ or -$CONHSO_2R^5$ where R^5 is not hydrogen, -tetrazol-5-yl, -

$NR^5C(=NR6)NR^5R^6$, $-C(O)N\ R^5OR^6$, $-SO_2NHCONR^5R^6$ or $-SO_2NHCN$;

or R^7 is phenyl or naphthyl, optionally substituted by R^1, R^2, R^3 and R^4 or a 5 to 6 membered heteroaryl group having 1 to 3 heteroatoms selected independently from N, O, and S and optionally substituted by R^1, R^2, R^3 and R^4;

or R^7 is C_3-C_6 cycloalkyl or 3-6 membered cycloheteroalkyl as defined above;

or R^7CH_2-N-A-, where A is as defined above, can form a non-aromatic 7-12 membered heterocyclic ring optionally containing an additional heteroatom selected from O, S and N wherein said heterocyclic ring may be optionally fused to another benzene ring;

R^8 and R^9 are independently H, aryl or heteroaryl as defined above, $-C_3$-C_7-cycloalkyl or cycloheteroalkyl as defined above, $-C_1$-C_4-perfluoroalkyl, straight chain or branched $-C_1$-C_6-alkyl, $-C_2$-C_6-alkenyl, or $-C_2$-C_6-alkynyl, each optionally substituted with hydroxy, alkoxy, aryloxy, $-C_1$-C_4-perfluoroalkyl, amino, mono- and di-C_1-C_6-alkylamino, carboxylic acid, carboalkoxy and carboaryloxy, nitro, cyano, carboxamido primary, mono- and di-C_1-C_6-alkylcarbamoyl;

a pharmaceutically acceptable salt thereof when one can be formed;
an optical isomer or diastereomer thereof.

2. A compound according to claim 1 wherein both of the carbons of A adjacent to the carbon bearing the sulfonamido group have a substituent other than hydrogen.

3. A compound according to claim 2 wherein the Z group is para-alkoxyphenyl, para-aryloxyphenyl or para-heteroaryloxyphenyl.

4. A compound according to claim 1 which is selected from the group consisting of:

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide,

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-8-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide,

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-bromo-quinoline-3-carboxylic acid hydroxyamide,

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-7-bromo-quinoline-3-carboxylic

acid hydroxyamide,

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide,

4-[(4-methoxybenzenesulfonyl)-pyridin-3-ylmethylamino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide,

4-[Benzyl-(4-methoxybenzenesulfonyl)-amino]-8-t-butyl-quinoline-3-carboxylic acid hydroxyamide,

4-[Benzyl-(4-methoxybenzenesulfonyl)-amino]-8-methyl-quinoline-3-carboxylic acid hydroxyamide,

8-Ethyl-4-[benzyl-(4-methoxybenzenesulfonyl)-amino]-quinoline-3-carboxylic acid hydroxyamide,

4-[Benzyl-(4-methoxybenzenesulfonyl)-amino]-8-(1-methylethyl)-quinoline-3-carboxylic acid hydroxyamide,

4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-8-vinyl-quinoline-3-carboxylic acid hydroxyamide,

4-[Benzyl-(4-methoxy-benzenesulfonyl)-amino]-6-nitro-quinoline-3-carboxylic acid hydroxyamide,

4-[Methyl-(4-methoxy-benzenesulfonyl)-amino]- 8-bromo-quinoline-3-carboxylic acid hydroxyamide,

4-{Methyl-[4-(pyridin-4-yloxy)-benzenesulfonyl]-amino}-6-iodo-quinoline-3-carboxylic acid hydroxyamide,

4-{Methyl-(4-(pyridin-4-yloxy)-benzenesulfonyl]-amino}-6-iodo-quinoline-3-carboxylic acid hydroxyamide hydrochloride,

4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-6-phenylethynyl-quinoline-3-carboxylic acid hydroxyamide,

4-[Methyl-(4-methoxy-benzenesulfonyl)-amino]-6-phenylethyl-quinoline-3-carboxylic acid hydroxyamide,

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]- 8-methoxy-quinoline-3-carboxylic acid hydroxyamide,

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]- 8-bromo-quinoline-3-carboxylic acid hydroxyamide,

4-[(4-methoxy-benzenesulfonyl)-pyridin-3-ylmethyl amino]-8-Benzyl-quinoline-3-carboxylic acid hydroxyamide,

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]- 8-iodo-quinoline-3-carboxylic acid hydroxyamide,

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-8-phenyl-quinoline-3-carboxylic acid hydroxyamide,

4-[(4-Methoxy-benzenesulfonyl)-pyridin-3-ylmethyl-amino]-8-thiophen-2-yl-quinoline-3-carboxylic acid hydroxyamide,

4-[(Biphenyl-4-sulfonyl)-pyridin-3-ylmethyl-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide,

4-[(Octane-1-sulfonyl)-pyridin-3-ylmethyl-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide,

4-[Pyridin-3-ylmethyl-(toluene-4-sulfonyl)-amino]-7-trifluoromethyl-quinoline-3-carboxylic acid hydroxyamide,

4-[Benzyl-(4-methoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin -3-ylmethylamino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide hydrochloride,

4-[Benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-1H-pyrazolo[3,4-b] pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin -3-ylmethylamino] -1-phenyl- 1H-pyrazolo[3,4b]pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin -3-ylmethylamino] -1-phenyl- 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide, hydrochloride,

4-[Benzyl-(4-methoxybenzenesulfonyl)amino]-1-phenyl-3-methyl-1H-pyrazolo[3,4b] pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1phenyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide, hydrochloride,

4-[(4-Methoxybenzenesulfonyl)pyridin-2-ylmethyl amino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-4-ylmethylamino] -1,3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino] -1-isopropyl - 1H-pyrazolo[3,4b]pyridin -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino] -1-benzyl-1H-pyrazolo[3,4-b] pyridin -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)amino] -1-benzyl -3-methyl -1H-pyrazolo[3,4-b] pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl) 2-thienylmethylamino] -1, 3- dimethyl - 1H-pyrazolo[3,4b]pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl) -3-thienylmethylamino] -1, 3- dimethyl - 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl) pyridin-3-ylmethylamino] -1- (2,4-dimethoxyphenyl) - 3- methyl- 1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino] -1-(2- methoxyphenyl)-3-methyl-1H-pyrazolo[3,4-b]pyridine -5-carboxylic acid, hydroxyamide,

4-{Methyl-[4-(4-pyridinyloxy)benzenesulfonyl]amino}-1,3-dimethyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylic acid, hydroxyamide,

4-{Methyl-[4-(phenoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide,

4-[Methyl-(4-methoxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide,

4-[Methyl-(4-propyloxybenzenesulfonyl)amino]-1,3-dimethyl-1H-pyrazolo[3,4-b] pyridine-5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-methyl-3-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-ethyl-3-phenyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide,

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-tert-butyl-3-methyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide and

4-[(4-Methoxybenzenesulfonyl)pyridin-3-ylmethylamino]-1-methyl-3-tert-butyl-1H-pyrazolo[3,4-b]pyridine-5-carboxylic acid, hydroxyamide.

5. A method of inhibiting pathological changes mediated by matrix metalloproteinases in mammals which comprises administration to a mammal in need thereof a therapeutically effective amount of a matrix metalloproteinase inhibiting compound according to claim 1.

6. A method according to claim 5 wherein the condition treated is atherosclerosis, atherosclerotic plaque formation, reduction of coronary thrombosis from atherosclerotic plaque rupture, restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, angiogenesis, tumor metastasis, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of

the liver, glomerular disease of the kidney, premature rupture of fetal membranes, infammatory bowel disease, or periodontal disease.

7. A method according to claim 5 wherein the condition treated is age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neovascularization and corneal graft rejection.

8. A method of inhibiting pathological changes mediated by TNF-α converting enzyme (TACE) in mammals which comprises administration to a mammal in need thereof a therapeutically effective amount of a TACE inhibiting compound according to claim 1.

9. The method according to claim 8 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, anorexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease, or HIV infection.

10. A pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a matrix metalloproteinase or TACE inhibiting compound according to claim 1.

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/US 97/18281

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/54 A61K31/47 C07D401/12 C07D409/14 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 606 046 A (CIBA-GEIGY AG) 13 July 1994 cited in the application see claims -----	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
25 February 1998	05.03.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/18281

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5-9
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 5-9
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/18281

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 606046 A	13-07-94	US 5455258 A	03-10-95
		AT 159012 T	15-10-97
		AU 684255 B	11-12-97
		AU 5265593 A	04-05-95
		CA 2112779 A	07-07-94
		DE 69314456 D	13-11-97
		FI 940012 A	07-07-94
		HU 70536 A	30-10-95
		JP 6256293 A	13-09-94
		MX 9400276 A	29-07-94
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